JANUARY 1972

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The American Journal of CARDIOLOGY

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OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Seminar on Clinical Application of Techniques to Measure Blood Flow in Man. Part I

ALBERTO BENCHIMOL, MD, FACC, Guest Editor

1

Advance Program
ACC 21st Annual Scientific Session

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In atrial fibrillation when normal sinus rhythm is established...

P24,097

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Contraindications: Same as for other forms of quinidine, including partial A-V or complete heart block; intraventricular conduction defects, especially marked QRS widening; sensitivity to quinidine; renal disease with significant azotemia; development of cardiotoxic effects (conduction defects or ventricular premature beats, ventricular tachycardia, or flutter) while taking the drug; marked cardiac enlargement with congestive failure; poor renal function with tubular acidosis.

Precautions: Same as for quinidine. To detect idiosyncrasy, e.g., febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment, administer preliminary test dose of single tablet of quinidine sulfate. Use extreme caution in patients with severe heart disease, congestive heart failure, digitalis intoxication, renal insufficiency. Administer cautiously, if at all, to senile patients. Hospitalization (for close observation, ECG monitoring and possibly plasma quinidine levels) indicated when administering large doses with patients presenting increased risk. With the dosage regimen (see "Dosage") of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm. Should not be used during pregnancy.

Adverse reactions: Instruct patients to report any symptoms of cinchonism at once (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, and respiratory distress); the drug should be discontinued immediately if such symptoms or evidence of hypotension occur. If gastrointestinal disturbances (rarely reported) occur, they may be minimized by administering the drug with food, or if they persist, dosage should be decreased.

Dosage: The dosage varies considerably depending upon the general condition and cardiovascular state of the patient. The quantity and frequency of administration must be determined for each patient. For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours. For maintenance of normal sinus rhythm following conversion by other techniques of atrial fibrillation, tachycardia or flutter, 2 tablets every 12 hours or 1½-2 tablets every 8 hours are usually required. The occasional patient may be maintained in normal rhythm on a dosage of 1 tablet every 12 or 8 hours. Occasionally larger or more frequent dosage may be required, but such increases should be used only after thorough evaluation of the patient, including serial electrocardiograms and determination of plasma quinidine levels. The ideal dosage is the minimum amount of total dose and frequency of daily administration that will prevent premature contractions, paroxysmal tachycardias, and maintain normal sinus rhythm.

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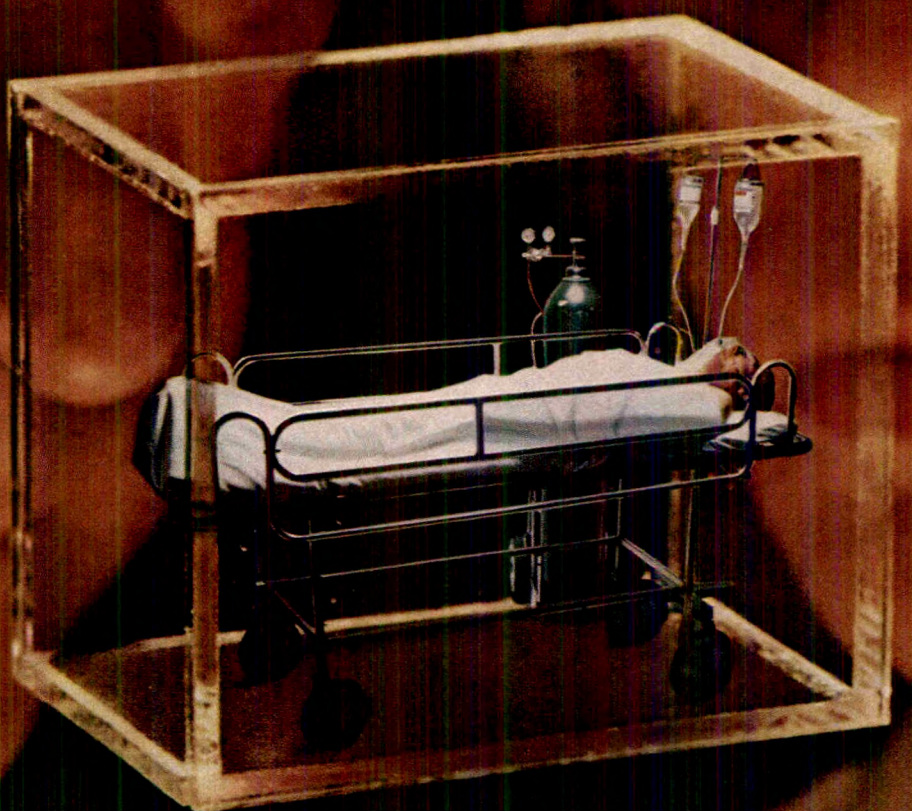

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test:

Confirms the value of Talwin® in the hospital

analgesic efficacy comparable to meperidine and morphine with a *minimum* of significant adverse effects

In postoperative patients: less circulatory depression with Talwin

In a double-blind study of 342 postop patients, circulatory depression occurred in 13.2% of 174 patients receiving morphine; in 5.4% of 168 patients receiving Talwin.[1]

. . . and in other patients: less respiratory and circulatory depression with Talwin

In a double-blind study of 3 narcotic analgesics and Talwin in 118* patients with suspected acute myocardial infarction, Talwin caused a significantly lower incidence in the fall of systolic blood pressure than the 3 narcotics when the initial pressure was 120 mm. Hg or higher. Unlike the narcotics, Talwin caused a statistically significant *rise* in the systolic blood pressure of patients with initial pressures of less than 120.[2]

In a study of a series of patients given Talwin or meperidine while anesthetized for surgery, the investigators concluded: "It would therefore appear that pentazocine is a much safer drug in respect of respiratory depression than pethidine [meperidine], particularly when repeated injections are to be given, e.g., postoperatively or in obstetric practice."[3]

. . . and less of other adverse effects associated with narcotic analgesics

Compared to morphine, Talwin is relatively free from urinary retention and constipation.

Is less likely to cause nausea, vomiting and diaphoresis than meperidine.

See next page for a complete discussion of adverse reactions and a brief summary of other Prescribing Information.

available in 3 dosage strengths—all within the range of recommended dosage

Talwin is available in 30 mg., 45 mg., and 60 mg. strengths to provide analgesia specific to patients' needs throughout the course of therapy. Most studies indicate that the higher dosage strengths produce little, if any, increase in the incidence of adverse reactions.

References: 1. Wallace, George: *Int. Surg. 53*:135, Feb. 1970.
2. Scott, M. E. and Orr, Rosemary: *Lancet 1*:1065, May 31, 1969.
3. Davie, I. *et al.*: *Brit. J. Anaesth. 42*:113, Feb. 1970.

*Other drugs studied: diamorphine and methadone.

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pentazocine
(as lactate)

bulwark against moderate to severe pain

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- **tolerance to analgesic efficacy has not been observed**
- **not subject to narcotic controls**

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor. Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, nodules and ulceration at injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.),* each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. Boxes of 10, 25, and 100.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide.

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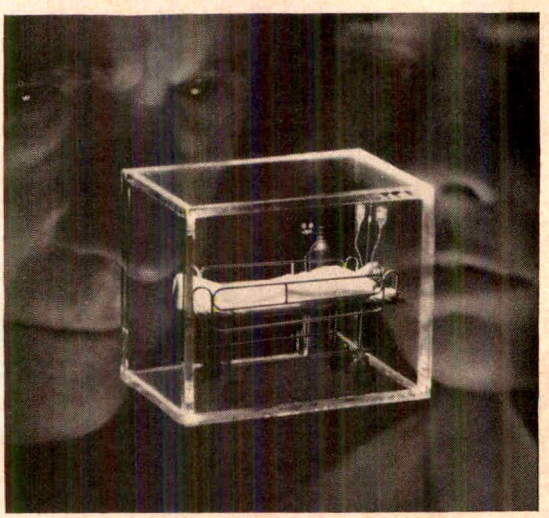

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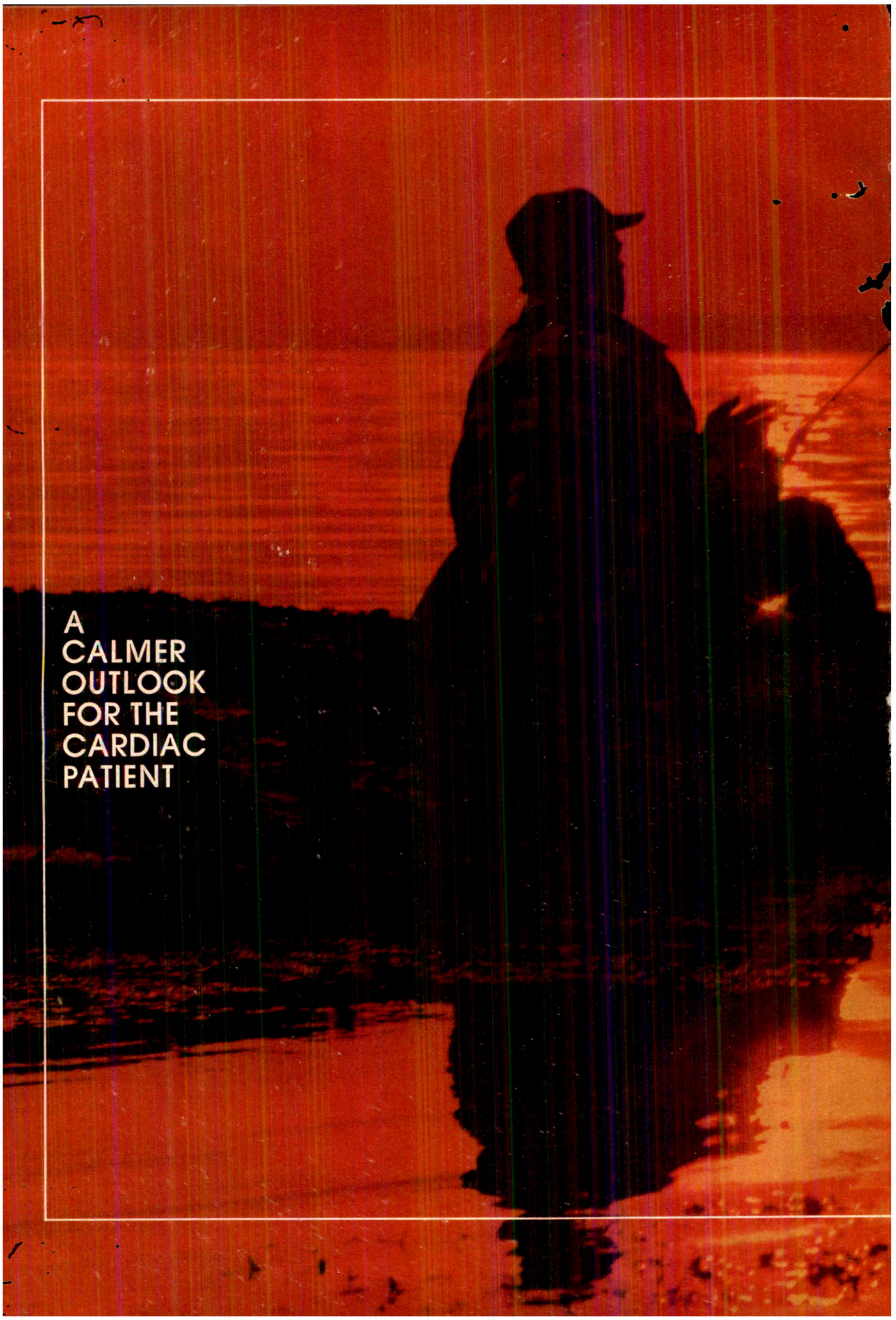
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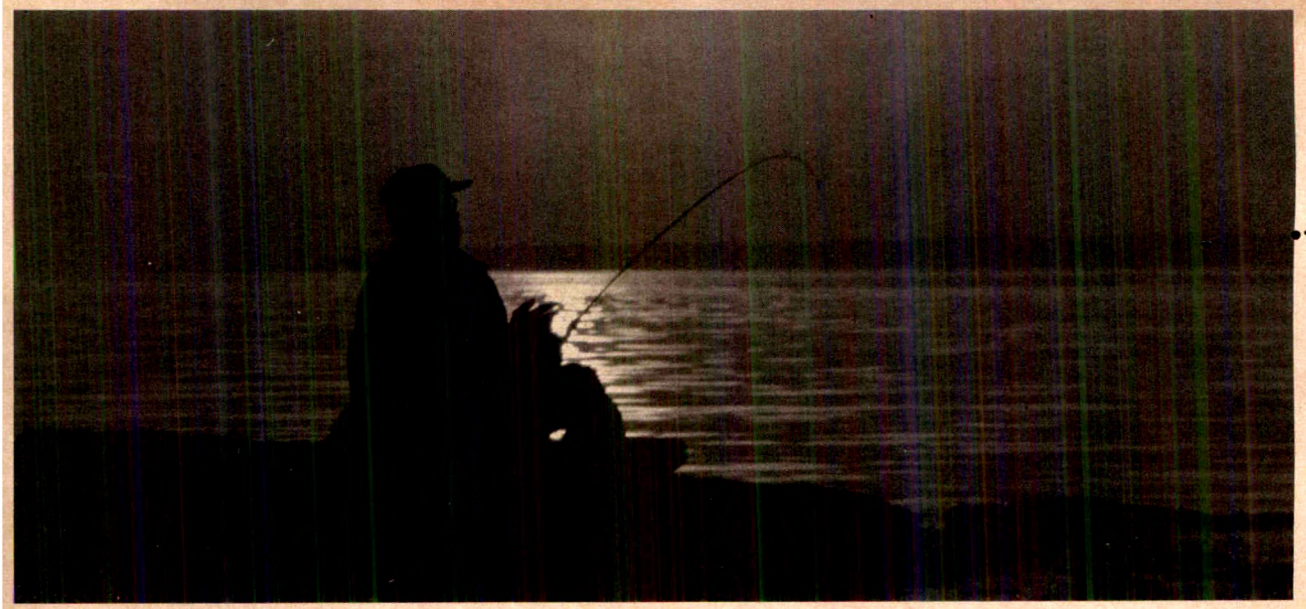

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Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use must not be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

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More detailed professional information available on request.

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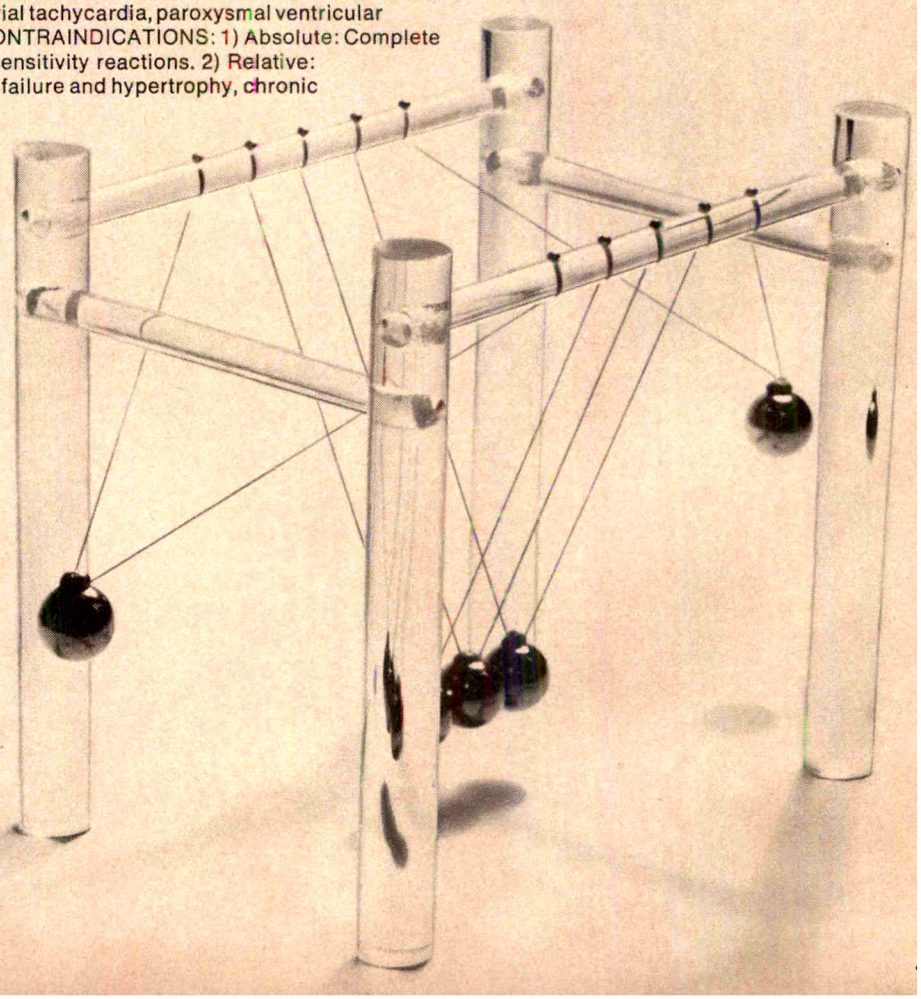

Alone among antiarrhythmics...

JANUARY 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 1

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CLINICAL STUDIES

1 **Ventricular Aneurysm. A Clinical-Pathologic Correlation**

ROGER W. DAVIS and PAUL A. EBERT

In a group of 40 patients with a left ventricular aneurysm after myocardial infarction the mean time from the initial infarction until formation of the aneurysm was 2.8 years and until death 4.8 years. All patients were symptomatic. Extensive coronary artery disease was found in all patients with ventricular aneurysm, indicating that coronary arteriography should be performed in these patients and that revascularization should probably be combined with excision of the dyskinetic segment.

7 **Coexisting Left Anterior Hemiblock and Inferior Wall Myocardial Infarction. Vectorcardiographic Features**

ALBERTO BENCHIMOL, KENNETH B. DESSER with the technical assistance of BETTIE JO MASSEY

Vectorcardiographic criteria (using the Frank system) for diagnosing coexisting left anterior hemiblock and inferior myocardial infarction include the following. Frontal plane: (1) clockwise and superior inscription of the 20 to 30 msec QRS vectors, (2) counterclockwise and delayed inscription of the terminal 40 msec QRS vectors, (3) maximal QRS vector located in the left superior quadrant, and (4) major area of QRS loop above the X axis. Sagittal plane: (1) superior inscription of the 20 to 30 msec QRS vectors, (2) deviation of the maximal QRS deflection vector superiorly and posteriorly, (3) delay in inscription of the terminal 40 msec QRS vectors, and (4) figure-of-eight or counterclockwise rotation of the QRS loop.

15 **Myocardial Lesions in Idiopathic and Alcoholic Cardiomyopathy. Study by Ventricular Septal Biopsy**

ROBERT T. BULLOCH, MALCOLM B. PEARCE, MARVIN L. MURPHY, B. J. JENKINS and JACK L. DAVIS

Electron and light microscopy studies of ventricular septal biopsies in 20 patients with cardiomyopathy showed that contractile element–sarcoplasmic reticulum disorganization and loss were consistent ultrastructural abnormalities that were common to both idiopathic and alcoholic cardiomyopathy and correlated with myocardial dysfunction. Generalized swelling of the sarcoplasmic reticulum without disorganization was an early manifestation of myocardial damage in alcoholic cardiomyopathy. Similar change was focal and inconsistent in idiopathic cardiomyopathy. This finding was the only consistent difference between alcoholic and idiopathic cardiomyopathy.

26 **Circulatory Responses to Beta Adrenergic Blockade with Alprenolol. Studies in Patients with Chronic Heart Disease**

RICHARD E. KERBER, ROBERT H. GOLDMAN, EDWIN L. ALDERMAN and DONALD C. HARRISON

The administration of 0.2 mg/kg body weight of alprenolol in 14 patients with acquired heart disease produced significant decreases at rest and during bicycle exercise in heart rate, cardiac index, dp/dt, left ventricular work and aortic systolic pressure and (during exercise alone) in tension-time index and mean systolic ejection rate. In these patients alprenolol had substantial negative chronotopic and inotropic effects similar to those of propranolol.

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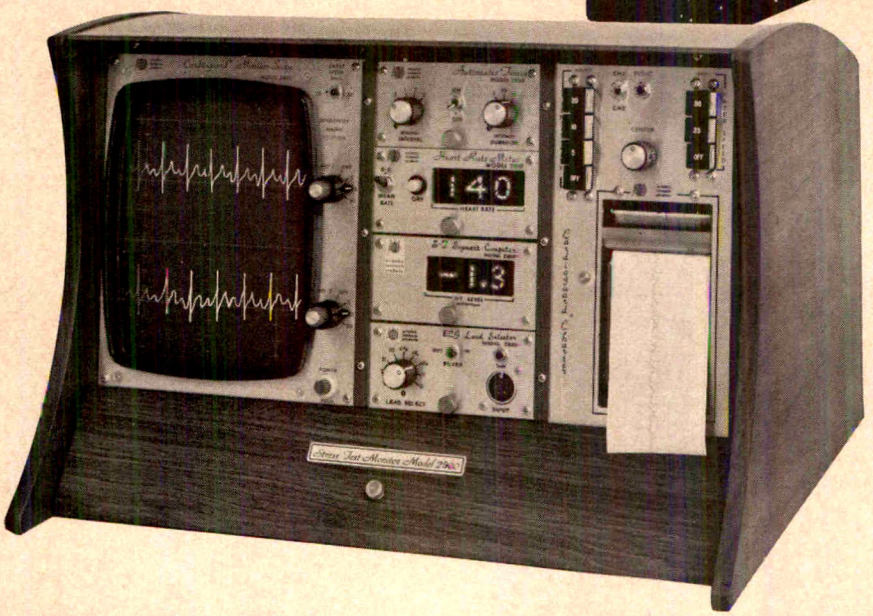

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33 **Dietary Salt and Essential Hypertension**

PAUL S. SWAYE, RAY W. GIFFORD, Jr. and J. N. BERRETTONI

No significant differences were found in this study between 717 patients with essential hypertension and 819 normotensive patients with regard to dietary history of salt consumption. However, the data suggest that dietary salt consumption may play a role in determining the severity of hypertension once it has developed.

39 **Myocardial Anaerobiosis in Anemia in Uremic Man**

BARBARA G. DELANO, ROBERT NACHT, ELI A. FRIEDMAN and NORMAN KRASNOW

Myocardial lactate balance studies demonstrated compensatory myocardial anaerobiosis in 6 young physiologically stable anemic uremic patients with a normal heart and no angina during 1 or more stressful situations. Cardiac index and systolic ejection rates indicated a hyperkinetic circulation at rest, increased by isoproterenol and exercise, and decreased by transfusion.

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47 **The Relation Between Myocardial ^{3}H-Digoxin Concentration and Its Hemodynamic Effects**

ROBERT N. DEUTSCHER, DONALD C. HARRISON and ROBERT H. GOLDMAN

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56 **Collateral Vessel Development After Right Ventricular Infarction in the Pig**

ROBERT H. PETER, BARRY W. RAMO, NORMAN RATLIFF and JAMES J. MORRIS, Jr.

Right ventricular hypertrophy and hypertension were induced in healthy farm pigs by pulmonary arterial banding which raised right ventricular systolic pressure from 24 to 74 mm Hg and doubled right ventricular mass in 4 weeks. The procedure made the right ventricle susceptible to infarction and impeded total collateral filling of the right coronary artery occluded by an ameroid constrictor.

REPORTS ON THERAPY

61 **Peritoneal Dialysis for Intractable Heart Failure in Acute Myocardial Infarction**

MONTE MALACH

Peritoneal dialysis was safely and effectively employed in 4 patients with intractable congestive heart failure during the course of acute myocardial infarction. Before dialysis, digitalis and potent diuretic agents failed to relieve pulmonary edema or reduce venous pressure, and oliguria increased.

REVIEWS

64 **The Effect of Age on the Electrocardiogram**

ERNST SIMONSON

Significant electrocardiographic age trends in adult healthy populations from the third to fifth decades include decreased QRS and T wave amplitudes, greater left axis shift and an increased incidence of premature supraventricular and ventricular beats. The vectorcardiogram shows age trends similar to those of comparable conventional electrocardiographic items. Implications are reviewed.

continued

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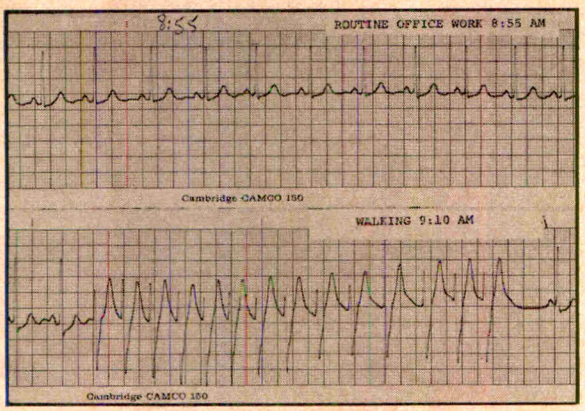

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74 **Introduction**

ALBERTO BENCHIMOL

75 **Techniques to Measure Coronary Blood Flow in Man**

RICHARD J. BING, ARMIN RICKART and KLAUS HELLBERG

This paper assesses currently useful methods to measure coronary blood flow in man. These include techniques utilizing diffusible gases, diffusible substances that actively enter the cell, continuous thermodilution and ultrasonic Doppler flowmeter. The measurements obtained provide fundamental insight into the behavior of the coronary circulation and influence basic and clinical concepts of ischemic heart disease.

FOUNDER'S LECTURE

81 **Prospects in Antithrombotic Therapy**

SOL SHERRY

This lecture reviews current concepts in the pathogenesis of acute coronary thrombosis, the rationale and prophylactic use of antiplatelet aggregating agents and the application of thrombolytic agents, (streptokinase and urokinase) in the treatment of acute myocardial infarction. Controlled therapeutic trials appear to be indicated in this most promising area of antithrombic therapy.

CASE REPORTS

90 **Mitral Valvular Abnormalities Associated with Supravalvular Aortic Stenosis. Observations in 3 Cases**

ANTON E. BECKER, MIES J. BECKER and JESSE E. EDWARDS

Although 3 of 5 patients with supravalvular aortic stenosis showed lesions of the mitral valve at postmortem study, it is uncertain whether these changes represent a coincidental or true association with supravalvular aortic stenosis.

75 **Malfunction of Mitral Ball Valve Prosthesis Due to Thrombus. Report of 2 Cases with Notes on Early Clinical Diagnosis**

JAMES PFEIFER, NORA GOLDSCHLAGER, THOMAS SWEATMAN, FRANK GERBODE and ARTHUR SELZER

Auscultation and phonocardiography demonstrating delay in the opening sound of the mitral valve and echocardiography showing delayed opening of the ball and delayed cage motion permitted the preoperative diagnosis of malfunction of a mitral ball valve prosthesis caused by ingrowth of fibrin clot in 2 patients. In both, reoperation was successful.

100 **Extralobar Pulmonary Sequestration. Presentation as an Arteriovenous Aneurysm with Cardiac Failure in Infancy**

ELTON GOLDBLATT, GRAHAM VIMPANI and J. HOWARD BROWN

An arteriovenous fistula with a large left to right shunt caused cardiac failure in an infant with extralobar pulmonary sequestration. A nonaerated pulsatile lobe of lung supplied by 2 systemic arteries arising from the aorta and passing through the hiatal ring was found at operation.

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Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.

Dosage: One capsule two or three times daily at 8 to 12 hour intervals.

Reference:

1. Master, A. M.: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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104 **Meningococcal Pericarditis. Report of 2 Cases, 1 Complicated by Acute Constrictive Pericarditis**

LEWIS P. SCOTT, DONALD KNOX, LOWELL W. PERRY and FRANCISCO J. PINEROS-TORRES

Two cases are reported of purulent pericarditis complicating meningococcal infection in children. In 1 patient acute constrictive pericarditis developed 1 month after pericardiocentesis for cardiac tamponade. Ampicillin is now the drug of choice in treating meningococcal pericarditis. Pericardiocentesis or pericardiostomy with drainage is mandatory if signs of pericardial compression or infection persist.

109 **Hypersensitive Carotid Sinus Syncope Treated by Implantable Demand Cardiac Pacemaker**

KURT VON MAUR, EDWARD W. NELSON, JAMES W. HOLSINGER, Jr. and ROBERT S. ELIOT

This report illustrates interesting successful use of a permanent demand cardiac pacemaker to prevent significant bradycardia and hypotension in a 43 year old man with hypersensitive carotid sinus syncope.

DIAGNOSTIC SHELF

111 **Observations on Second Degree Atrioventricular Block, Including New Criteria for the Differential Diagnosis Between Type I and Type II Block**

RICHARD LANGENDORF, HOWARD COHEN and EDILBERTO G. GOZO, Jr.

Depression of conduction below the atrioventricular (A–V) node tends to produce type II second degree heart block in contrast to the occurrence of type I block when A–V nodal conduction is depressed. However, type I block can also develop in the His bundle and in the bundle branches. In type I concealed conduction occurs within the region of the block and depresses subsequent conduction. In type II concealed conduction occurs down to the region of the block discharging subsidiary functional pacemakers and preventing their escape. Type II block is frequently associated with bundle branch block and ventricular escapes with normal retrograde conduction (unidirectional block).

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E. E. EDDLEMAN, Jr., WALTER K. HARRISON, DAVID H. JACKSON and HENRY L. TAYLOR

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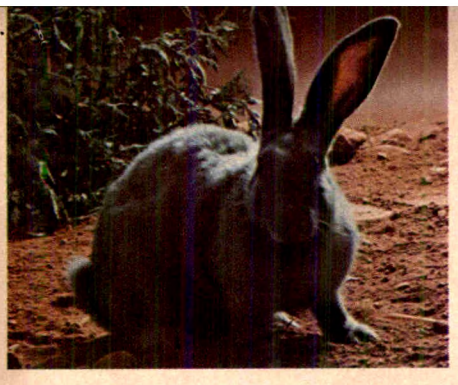

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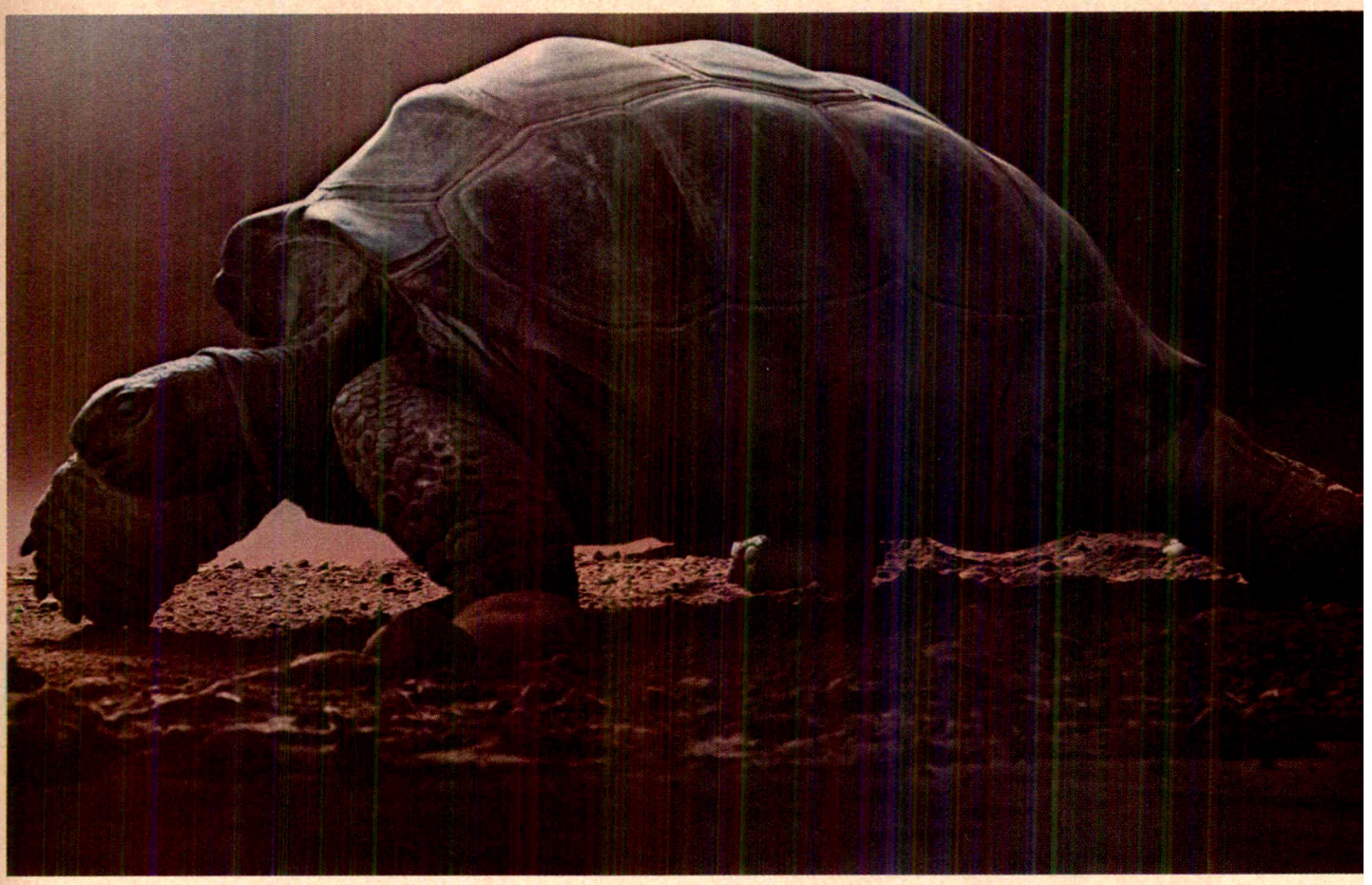

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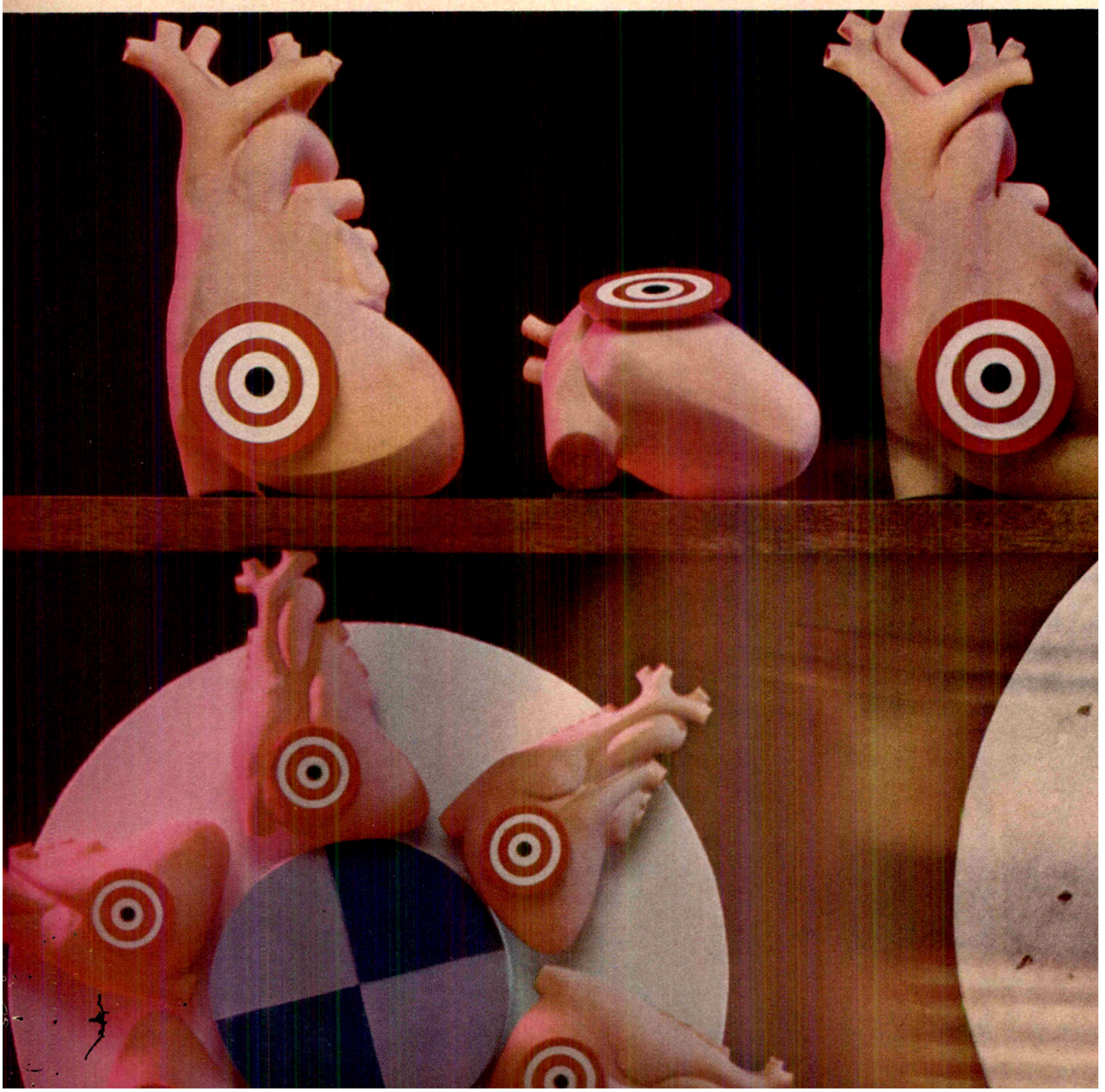

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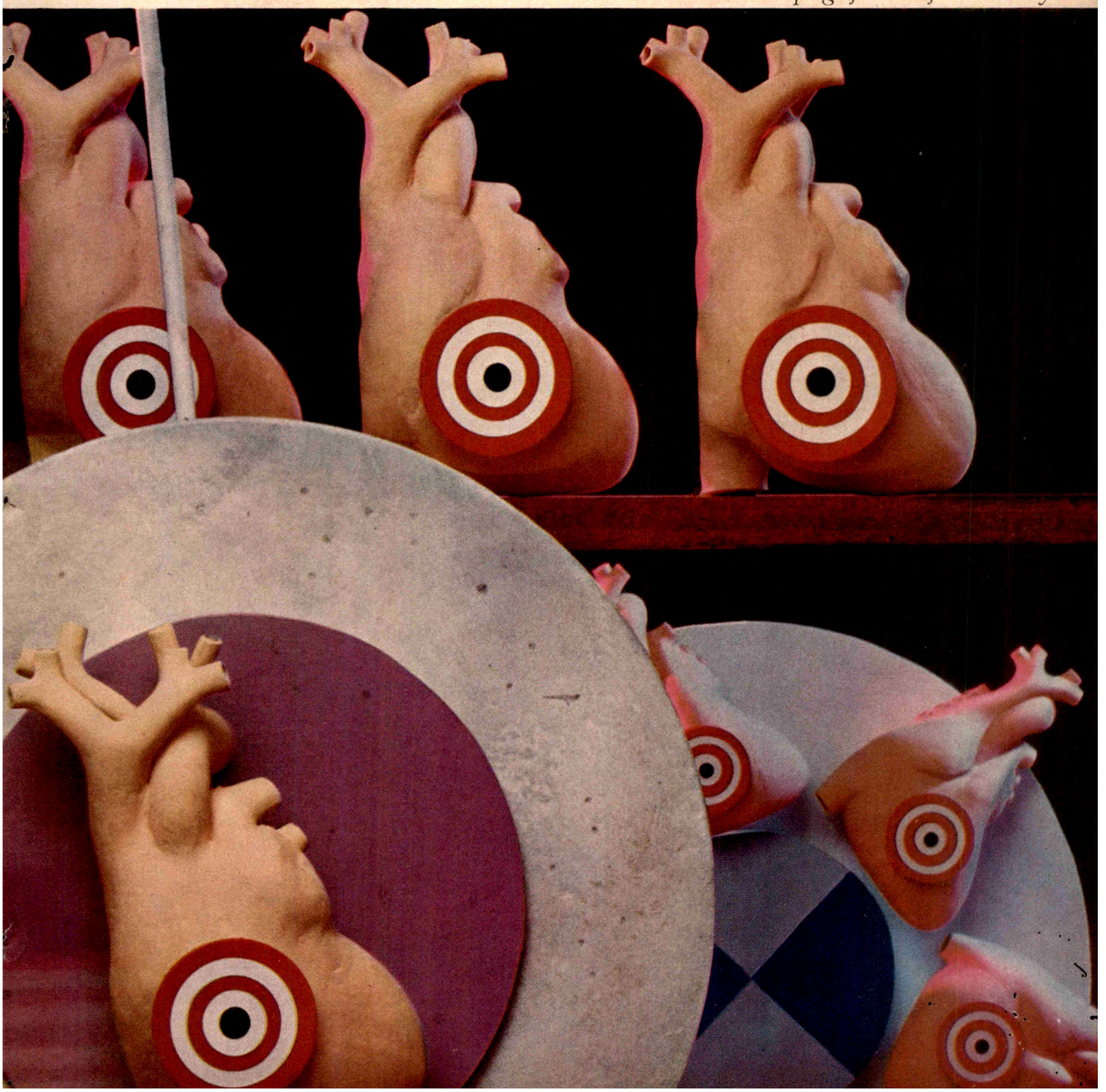

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Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 Gm. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. If any sign of lupus erythematosus occurs, LE cell tests should be performed; if cell tests are positive, discontinue drug. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide. Tests at regular intervals for lupus erythematosus are recommended for patients on maintenance therapy.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

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Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When Dyrenium (triamterene, SK&F) is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Supplied: 100 mg. capsules in bottles of 100.

1. Ross, E.J.: Aldosterone and Its Antagonists, *Clin. Pharmacol. & Therap.* 6:65 (Jan.-Feb.) 1965.
2. Earley, L.E.: Edema Formation and the Use of Diuretics, *California Med.* 114:56 (Mar.) 1971.

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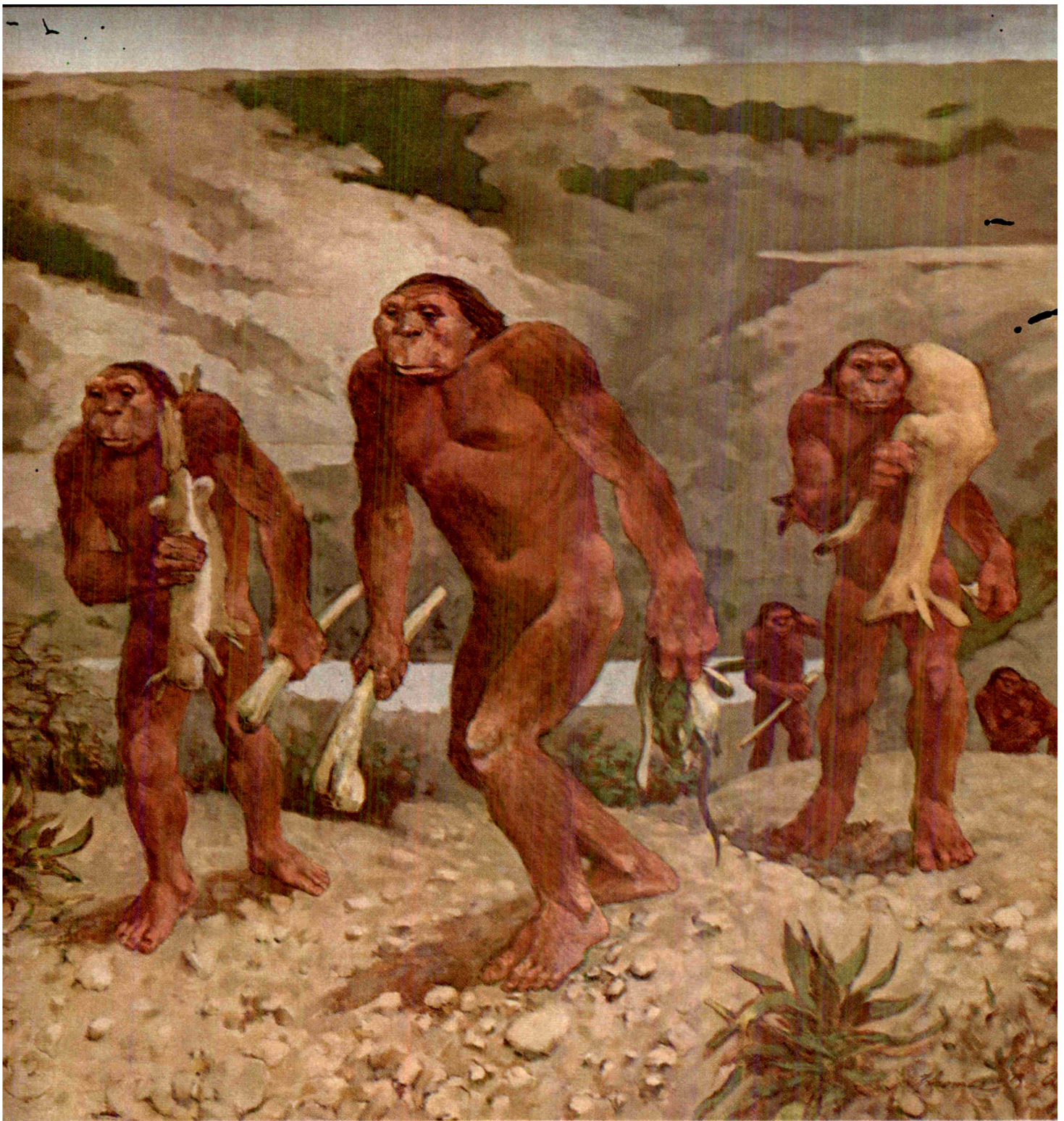
DY-202



Beginning of our hyperlipidemic way of life

One million years ago, a primitive ancestor of man assumed a meat-eating habit which he passed on to his descendants. According to Collens,[1] "... man has indulged himself in eating foods containing large amounts of cholesterol and saturated fats, although he does not have the anatomic and physiologic capabilities for handling these foods in a manner comparable to carnivores." As stated editorially in *Lancet*,[2] "the 'unnatural' diets of Western man are associated with a high proportion of saturated fatty acids in the blood...." Also, a large intake of carbohydrates cannot be overlooked as a contributory factor in hyperlipidemia.[2,3]

...today

One of five Americans over the age of seventeen has a serum cholesterol level of 260 mg./100 ml. or higher, according to the U.S. Public Health Service.* Stamler *et al.*[3] state: "A significant proportion of our population is frankly hypercholesterolemic." They further report that among the millions of adult Americans with this condition, a majority are entirely unaware of its presence because they have never been tested for it.

*Based on mean averages obtained by examining 6,670 persons out of a sample of 7,700. This group represented 111 million adults in the target population. Adapted from U.S. Public Health Service Publication, March, 1967.[4]

See last page of advertisement for prescribing information.

Ayerst®

The determination of serum lipids

Recently, considerable interest has been shown in the classification of primary hyperlipidemia into five types by Fredrickson and associates.[5] The following chart shows that in three of the four most commonly seen types, triglycerides as well as cholesterol may be elevated. Therefore, triglycerides are also important in making the diagnosis of primary hyperlipidemia.
In studies on 1,000 age-controlled patients, Fredrickson found that hyperlipidemia will be detected in 96 per cent of cases if both serum cholesterol and triglyceride determinations are performed.[7]

Classification of primary hyperlipidemia*

Type	Lipoprotein	Triglycerides	Cholesterol	Carbohydrate Sensitive	Fat Sensitive
I (rare)	Chylomicra elevated	Elevated	Normal	No	Yes
II	Beta lipoproteins elevated	Normal	Elevated	No	Yes
III	Abnormal Beta lipoproteins present	Elevated	Elevated	Yes	Yes
IV	pre-Beta lipoproteins elevated	Elevated	Normal or Elevated	Yes	No
V	Chylomicra and pre-Beta lipoproteins elevated	Elevated	Elevated	Yes	Yes

*Adapted from Fredrickson's 5 Major Categories of Primary Hyperlipidemia.[5]

Atromid-S® (clofibrate)

For the significant reduction of elevated levels of cholesterol and/or triglycerides

Adequately repeated base line studies should be performed to determine if the patient has a significantly elevated serum lipid level. When cholesterol and/or triglyceride levels are found to be elevated, an attempt should first be made to control them with an appropriate dietary regimen.[6] When response is inadequate, lipid-lowering therapy should be initiated with ATROMID-S.
With ATROMID-S therapy:
• you can expect elevated serum cholesterol and/or triglyceride levels to be lowered in responsive patients during the first month of treatment. • you can also expect that the higher the initial level, the greater the fall
In xanthomatosis, a reduction in size and/or number of lesions is an indication of response to therapy, and the drug should be administered for an extended period of time, even up to one year.

AN IMPORTANT NOTE: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

The most widely prescribed lipid-lowering agent with seven years of clinical experience

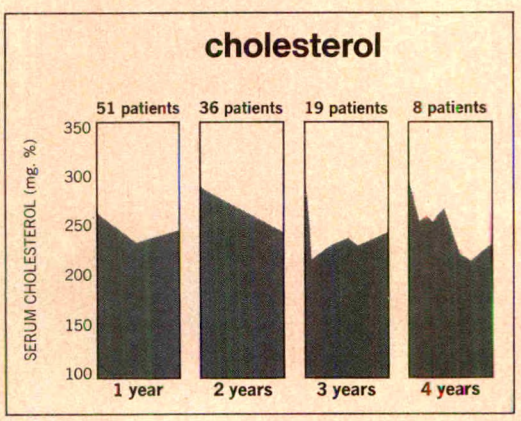
Sustained long term reduction of elevated serum lipid levels with Atromid-S (clofibrate)

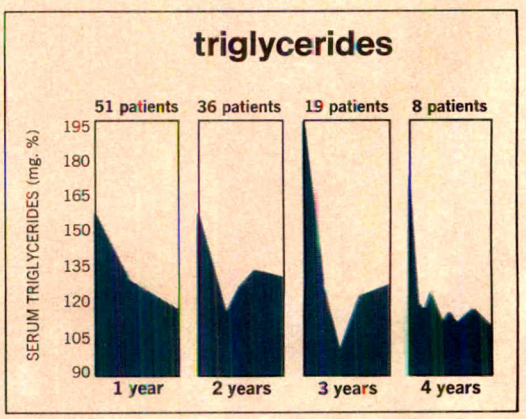
In responsive patients who received ATROMID-S continuously, and who were studied for periods ranging from six months to four years, the lipid-lowering effect was sustained throughout therapy.[8-15]

It has been shown, that lipids return to pretreatment levels when ATROMID-S is discontinued.[8,9,14] According to Oliver,[14] "this clearly indicates the need for continued treatment."

Long term effectiveness*

Of a total of 133 patients treated, there were 114 responders and 19 nonresponders. There were 51 responders in the one year therapy group; 36 responders in the two year group; 19 responders in the three year group; and 8 responders in the four year group.
*Adapted from Oliver.[9]



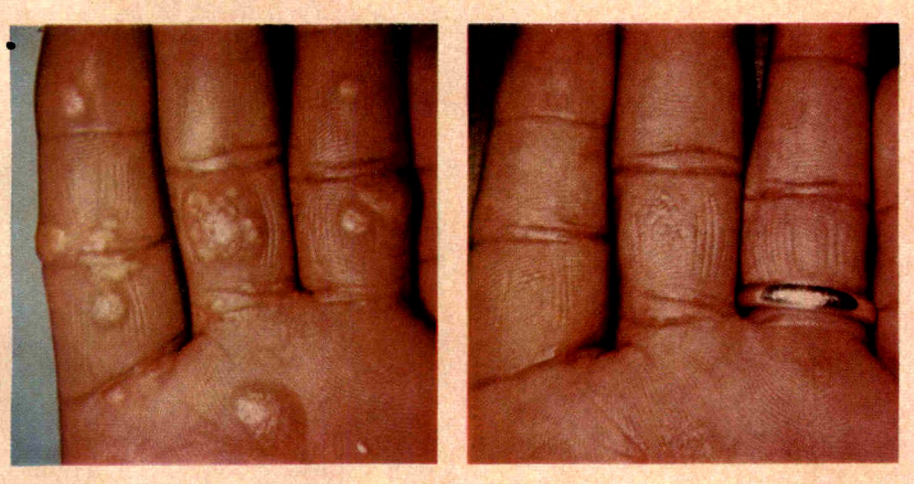


Visible evidence of effectiveness

Oliver[16] is among several investigators who have reported the regression of xanthomata in patients treated with ATROMID-S (clofibrate). This demonstration of regression of xanthomata with ATROMID-S provides visible evidence of the effectiveness of this agent. In some patients, xanthomatous lesions completely disappeared;[9,11,17-19] and in others their size and/or numbers have been reduced.[9-11,19-21]

Regression of xanthomata demonstrated

Before therapy **After therapy**



Male, 39 years old, with long-standing xanthomatous lesions involving elbows, knees, palms and palmar surfaces of the fingers, and buttocks.

Laboratory Data†

2/25/69	cholesterol: 544 mg.%
	triglycerides: 315 mg.%
3/11/69	ATROMID-S therapy instituted
9/26/69	cholesterol: 289 mg.%
	triglycerides: 129 mg.%

Lesions on palms have disappeared completely. Lesions on elbows and knees are smaller and softer.

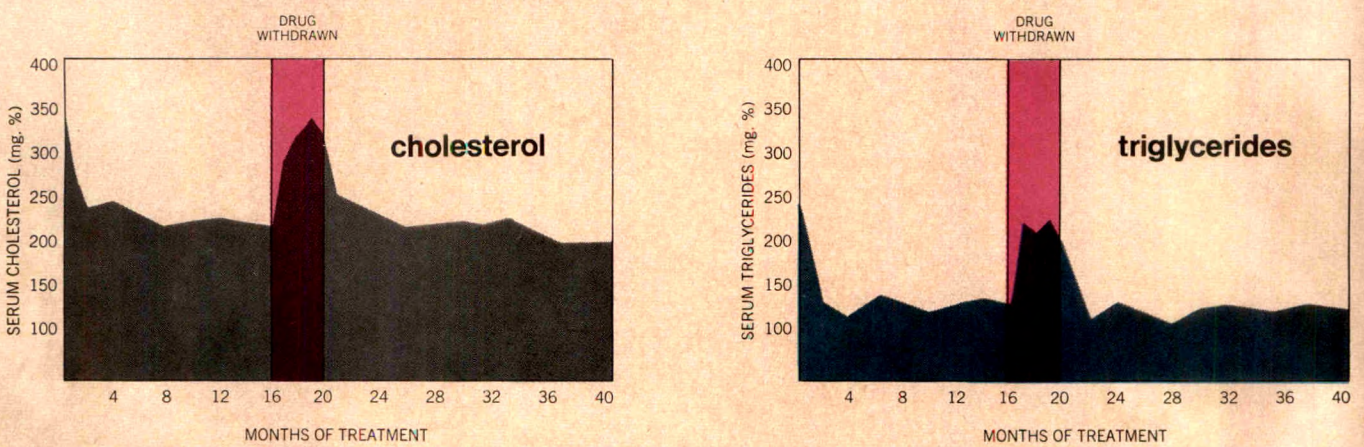
†Case report on file, Medical Department, Ayerst Laboratories, New York, N.Y.

To maintain the lipid-lowering effects—maintain the recommended dosage

One dosage regimen—one capsule Q.I.D.—for all patients at all times. After lipid levels have been reduced, maintain the recommended dosage. A reduction in dosage may result in a rise in lipid levels.

If treatment is interrupted

The interruption of therapy when the patient is under control would permit lipid levels to return to their original pretreatment status. Berkowitz[13] demonstrated the effect of interrupted therapy in the 40 month patient study shown below.



Patient received ATROMID-S (2 Gm. daily) for the first 16 months. Between the 16th and 20th month, therapy was withdrawn completely. From the 20th to the 40th month, ATROMID-S therapy (2 Gm. daily) was resumed.

If given in conjunction with anticoagulants

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

See following page for prescribing information.

Ayerst®

For the reduction of elevated serum cholesterol and/or triglyceride levels

Atromid-S® (clofibrate)

start and maintain therapy with one capsule Q.I.D.

BRIEF DISCUSSION SUMMARY

Indications: ATROMID-S is indicated where reduction of serum lipids is desirable, *e. g.*, patients with hypercholesterolemia and/or hypertriglyceridemia.

Patients with hyperlipemic states involving elevation of both serum triglycerides and serum cholesterol generally have a more favorable response than those with primarily hypercholesterolemia and normal triglyceride levels. However, since response is unpredictable, a therapeutic trial with ATROMID-S should be undertaken in patients with only hypercholesterolemia.

In patients with essential hyperlipemia and xanthomatosis, the skin lesions frequently have regressed on ATROMID-S therapy.

Contraindications: While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

Young women with familial hyperlipemia should not be deprived of this drug, and its use in nonpregnant women in the childbearing age may be undertaken in patients exercising strict birth control procedures. In patients who then plan to become pregnant the drug should be withdrawn several months before conception.

Because pregnancy is a possibility despite birth control precautions, the possible benefits of clofibrate to the patient must be weighed against possible hazards to the fetus in women of childbearing age. Since it is not known if clofibrate is secreted in human milk, the drug should not be given to lactating women.

This drug is not, as yet, indicated for use in children since studies in children have been insufficient.

It is not recommended for use in patients with impaired renal or hepatic function.

Warnings: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE) . THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

Precautions: Before instituting clofibrate therapy, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be made during the first few months of ATROMID-S (clofibrate) administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, treatment should be continued for longer periods (even up to one year) provided there is a reduction in the size of the xanthomata.

During the early stages of ATROMID-S administration, serum transaminase determinations should be made. Mild transient increases in these tests have been noted in some patients. This is thought to be a result of the metabolic effect of the drug rather than a toxic effect. However, if steadily rising or excessive abnormalities occur, the drug should be immediately withdrawn.

Studies in diabetic patients given clofibrate have failed to indicate any effect on insulin or oral hypoglycemic requirements. However, one investigator reported an episode of hypoglycemia occurring two hours after ingestion of 1 Gm. of clofibrate in a patient receiving tolbutamide. Although a causal effect was not established, caution should be observed in diabetic patients.

Adverse Effects: ATROMID-S (clofibrate) has been well tolerated by most patients. The most common side effect is nausea, noted in approximately 5 per cent of cases. Other less common gastrointestinal side effects include vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Headache, dizziness, fatigue, weakness, skin rash, urticaria, pruritus, stomatitis have been reported occasionally. A slight and transient rise in serum glutamic oxaloacetic and/or glutamic pyruvic transaminases has been observed in some patients, but there is no evidence to suggest that this is due to hepatotoxicity. A few instances of increased BSP retention have been reported. One patient receiving butobarbitone, phenobarbital, phenindione, tetracycline, and clofibrate developed agranulocytosis which was attributed by the investigator to the clofibrate. A few cases of leukopenia have been reported, but relationship to ATROMID-S administration has not been established.

Polyphagia and weight gain have been noted in a few patients. It has been suggested that this may be due to increased deposition of subcutaneous fat. However, this has not been established nor has it been definitely determined that the weight gain is drug-related. Instances of weight loss have also been reported. One investigator reported congestive heart failure in a few patients on clofibrate. However, subsequent study by this investigator has shown no increase in circulating plasma volume.

Several instances of muscle cramping, aching, or weakness were reported. One patient with muscle cramps also showed a concomitant rise in SGOT. A few female patients have reported (reversible) dry, brittle hair. Three cases of alopecia areata occurring during ATROMID-S administration have been reported; relationship to this drug has not been established.

Dosage and Administration: *For adult usage only*. The recommended dose is one capsule (500 mg.) four times daily.

Supplied: No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Collens, W. S.: Med. Counterpoint *1*:53 (Dec.) 1969. 2. Editorial: Lancet *i*:1414 (June 29) 1968. 3. Stamler, J., *et al.*: Amer. J Nurs. *66*:1788 (Aug.) 1966. 4. U.S. Public Health Service Pub. Series 11, No. 22 (Mar.) 1967. 5. Fredrickson, D. S., Levy, R. I., and Lees, R. S.: New Eng. J. Med. *276*:34, 94, 148, 215, 273 (Jan. 5, 12, 19, 26, and Feb. 2) 1967. 6. Fredrickson, D. S.: Hosp. Pract. *3*:54 (June) 1968. 7. Fredrickson, D. S.: Paper presented at the 41st Scientific Session of the American Heart Association Meeting, Miami Beach, Fla., Nov. 23, 1968. 8. Gelfand, M. L., and Garber, M.: The Effect of Clofibrate on Hyperlipidemia. Exhibit, The Medical Society of New Jersey Annual Meeting, May 17-21, 1969. 9. Oliver, M. F.: Drugs Affecting Plasma Lipids—The Current Status of Ethyl Chlorophenoxyisobutyrate (Atromid-S) in Paoletti, R., Steinberg, D., and Kritchevsky, D.: Progress in Biochemical Pharmacology Basel/New York, S. Karger, 1967, vol. 2, pp. 315-324. 10. Duncan, G. G., *et al.*: Metabolism *17*:457 (May) 1968. 11. Mishkel, M. A.: Quart. J. Med. *36*:107 (Jan.) 1967. 12. Danowski, T. S., *et al.*: Clin. Pharmacol. Ther. *7*:631 (Sept.-Oct.) 1966. 13. Berkowitz, D.: Hyperlipidemia, Exhibit, A.M.A. Annual Convention, Atlantic City, June 18-22, 1967. 14. Oliver, M. F.: Practitioner *192*:424 (Mar.) 1964. 15. Hunninghake, D. B., Tucker, D. R., and Azarnoff, D. L.: Circulation *39*:675 (May) 1969. 16. Oliver, M. F.: Bull. N.Y. Acad. Med. *44*:1021 (Aug.) 1968. 17. Peak, H. J., Mitchell, A. S., and Jose, A. D.: Med. J. Aust. *2*:192 (July 31) 1965. 18. Brown, D. F., and Doyle, J. T.: Amer. J. Clin. Nutr. *20*:324 (Apr.) 1967. 19. Roe, D. A.: Arch. Derm. *97*:336 (Apr.) 1968. 20. Albert, M., and Stansell, M. J.: Metabolism *18*:635 (Aug.) 1969. 21. Nahum, L. H.: Conn. Med. *32*:506 (July) 1968.

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JANUARY 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 1

Clinical Studies

Ventricular Aneurysm

A Clinical–Pathologic Correlation

ROGER W. DAVIS, MD
PAUL A. EBERT, MD

Durham, North Carolina

The effect of formation of aneurysm on the course of patients with myocardial infarction has not been well established. Forty patients at this institution were diagnosed as having a left ventricular aneurysm following myocardial infarction from 1946 through 1968. All cases were reviewed, and the clinical course was carefully outlined. Twenty-four cases were confirmed at autopsy.

The mean time from the initial infarction until formation of aneurysm was 2.8 years and until death was 4.8 years. All patients with aneurysm were symptomatic, 85 percent with congestive heart failure, 65 percent with angina and 41 percent with some form of arrhythmia. Only 2 patients had clinically suspected arterial embolization.

Autopsy findings revealed extensive coronary artery disease in all patients. The aneurysms were variously placed in the left ventricle and averaged 5 cm in diameter; none was greater than 3 mm in wall thickness. Mural thrombi were found in 44 percent of the aneurysms.

The finding of extensive coronary artery disease in all patients with ventricular aneurysm emphasizes that coronary arteriography should be performed in this group and that revascularization probably should be combined with excision of the dyskinetic segment.

The success of surgical procedures to increase blood flow to the coronary circulation in patients with arteriosclerotic heart disease has resulted in an increased number of cardiac diagnostic procedures being performed. A dyskinetic or aneurysmal enlargement of the left ventricle is being observed more frequently in patients with few, if any, symptoms of cardiac failure. Surgical resection of left ventricular aneurysms even in the presence of profound cardiac failure has been associated with a low mortality rate and usually a dramatic relief of heart failure. With the low surgical mortality rate associated with resection of ventricular aneurysms, the possibility of a more liberalized approach to resection of dyskinetic or aneurysmal areas must be considered in pa-

From the Department of Surgery, Duke University Medical Center, Durham, N. C. 27706. Manuscript received January 29, 1971, accepted March 25, 1971.

Address for reprints: Roger W. Davis, MD, Department of Surgery, Duke University Medical Center, Durham, N. C. 27706.

TABLE I

Temporal Data in Cases of Aneurysm

Period	Mean Time (years)
From diagnosis of MI until diagnosis of aneurysm*	2.8 (0 to 18.9)
From diagnosis of aneurysm until death	3.9 (2 weeks to 12.0 years)
From diagnosis of MI until death*	4.8 (1 week to 18.9 years)

* Does not include 4 patients who had no documented history of myocardial infarction.
MI = myocardial infarction.

tients with an established diagnosis and minimal symptoms of heart failure. The sequence of events following myocardial infarction leading to the development of a ventricular aneurysm is well established.[1-6] The natural history of patients with a ventricular aneurysm who are without symptoms is not so well documented. The present study reviews the clinical course of patients with aneurysm of the left ventricle from the time of diagnosis until death or surgical intervention.

Materials

Hospital records of patients admitted to Duke University Medical Center from 1946 through 1968 were reviewed, and 40 patients were found to have had a ventricular aneurysm. The presence of ventricular aneurysm was accepted by a previous history of myocardial infarction followed by sequential evidence of left ventricular enlargement. The latter was documented by fluoroscopic examination with sequential cardiac series in 4 patients and by left ventricular cineangiography in 12 patients. In the 4 patients not studied by cineangiography, fluoroscopic evidence of lack of movement of the anterolateral wall was the criterion used to diagnose ventricular aneurysm. In the remaining 24 patients the diagnosis was confirmed at autopsy, and in only 6 of these had the clinical diagnosis been made before death. Of the remaining 18 patients, the sequence of events leading to the development of the aneurysm was reconstructed from the past medical history and the hospital record. In all, there were 5 female and 35 male patients ranging in age from 42 to 89 years (average 59 years).

Results

Clinical course: The average time from the occurrence of myocardial infarction to diagnosis of the aneurysm was determined to be 2.8 years. The average length of survival from the time of occurrence of myocardial infarction was 4.8 years and from the time of diagnosis of the aneurysm, 3.9 years (Table I). The radiologic sequence of the development of a ventricular aneurysm is shown in Figures 1 and 2. Figure 3 demonstrates 2 other roentgenographic presentations of ventricular aneurysm. Signs of congestive heart failure eventually developed in 85 percent of the patients. In 4 patients the time of myocardial infarction could

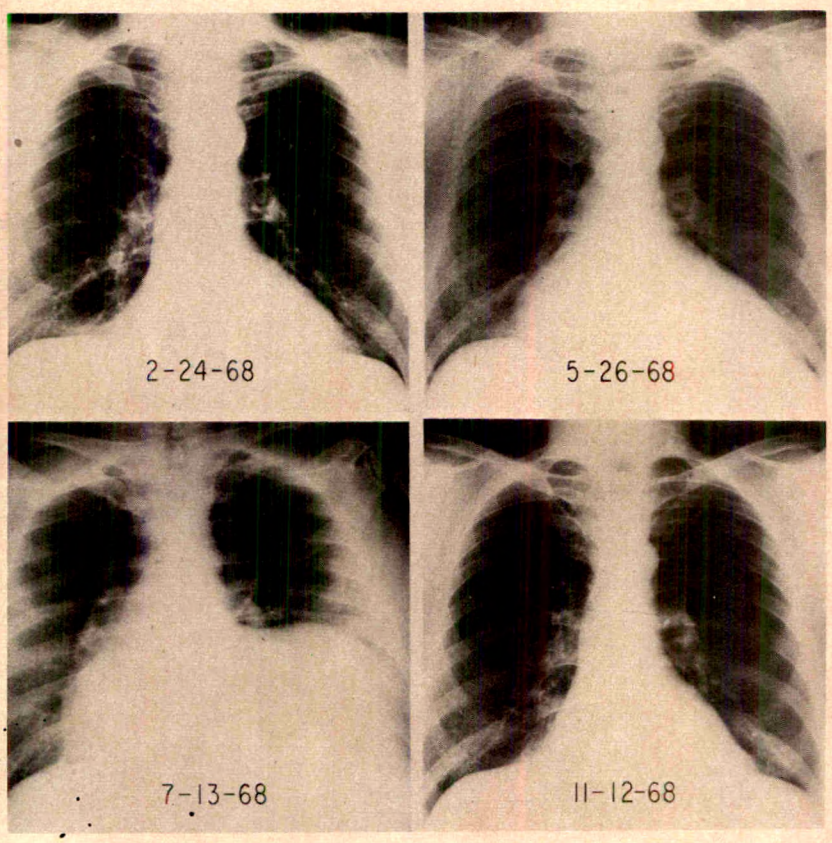

Figure 1. Roentgenograms showing development of a large left ventricular aneurysm in a 46 year old man. **Upper left,** taken immediately after his myocardial infarction; **lower right,** 3 months after successful aneurysmectomy.

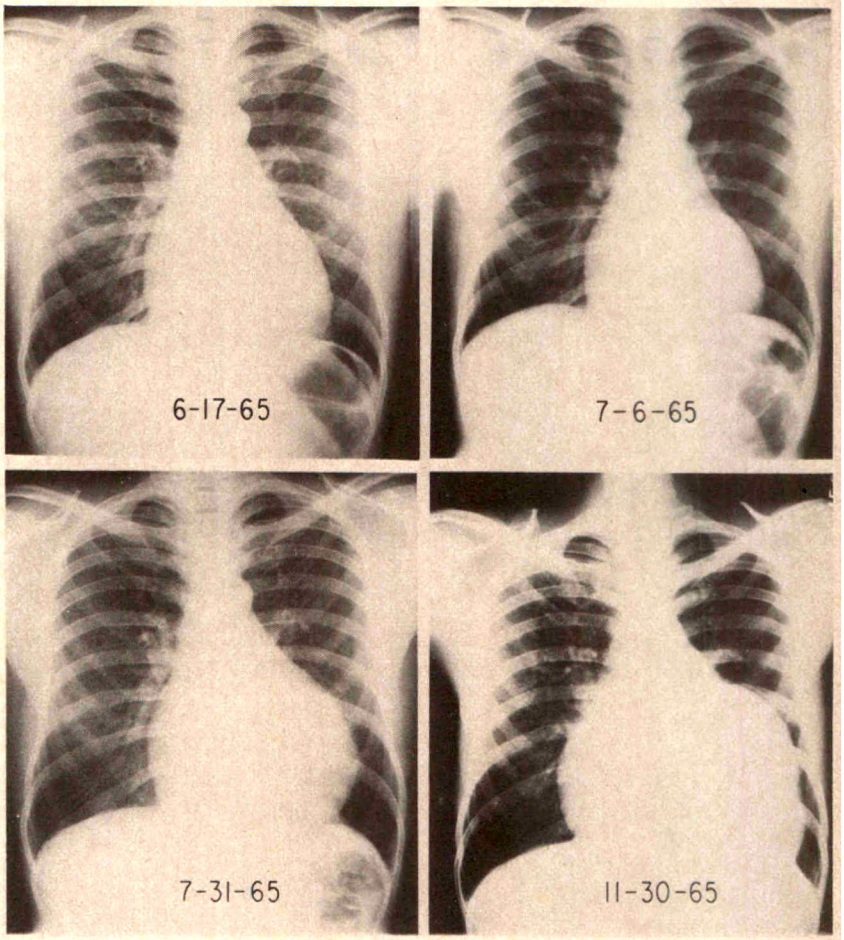

Figure 2. Roentgenograms showing progressive cardiomegaly after a diaphragmatic myocardial infarction in June 1965. During the postinfarction course severe congestive heart failure and mitral insufficiency developed. A 5 by 5 cm diaphragmatic aneurysm was noted on the ventriculogram. Chest roentgenograms were interpreted as showing only cardiomegaly except for the film of November 30, 1965, which was considered diagnostic of ventricular aneurysm.

not be documented, and no correlation could be made with development of ventricular aneurysm. Angina was present in 64 percent and some type of cardiac arrhythmia in 41 percent. Peripheral arterial embolization was documented in 2 patients. One aneurysm was found to have ruptured at postmortem examination.

Electrocardiograms: The findings were typical of previous myocardial infarction. Thirteen patients had persistent ST–T wave changes with diminished R waves in the precordial leads that were considered compatible with ventricular aneurysm (Fig. 4 and 5). The remaining tracings were compatible with chronic myocardial infarction, with 14 of these also showing evidence of recent infarction. Left bundle branch block was noted in 4, right bundle branch block in 1, and peri-infarction block in 3.

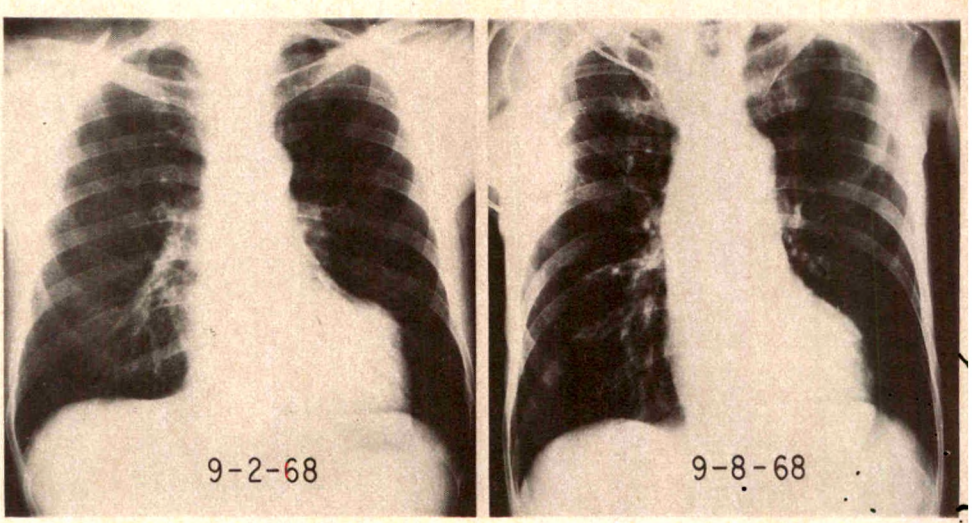

Figure 3. Roentgenograms. **Left,** classic findings of a discrete left ventricular aneurysm. **Right,** film from a patient who at autopsy was found to have diffuse thinning and aneurysmal dilatation of the entire apical region of the left ventricle.

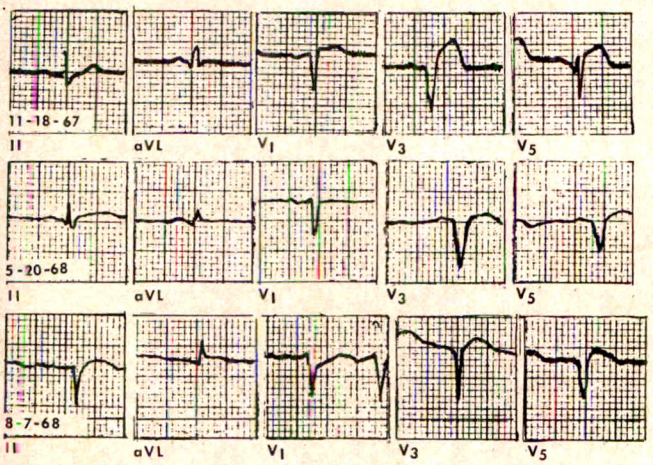

Figure 4. Representative electrocardiographic leads from a 46 year old white man at the time of initial myocardial infarction (November 18, 1967); 6 months after infarction (May 20, 1968) with no evidence of aneurysm formation; and 1 month after development of a large apical aneurysm. Note the S–T segment changes in the tracing of August 7, 1968.

Surgery: Four patients underwent surgery and had successful resection of the ventricular aneurysm with marked diminishing of cardiac failure. Three patients with ventricular aneurysm required some type of operative procedure unrelated to the heart, and all 3 died in the immediate postoperative period from circulatory failure.

Cause of death: This was ascertained in 27 patients. Sixteen had recurrent myocardial infarctions; 2 died of intractable heart failure; and 3 additional patients died of circulatory failure

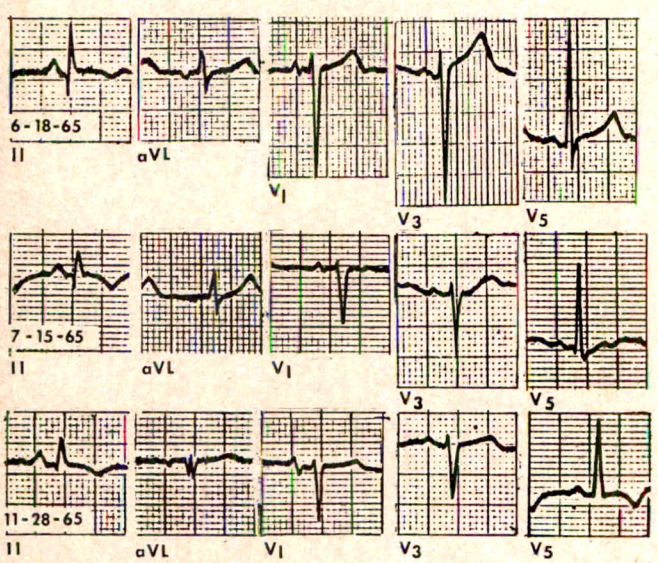

Figure 5. The electrocardiographic strips of June 18 and July 15, 1965 demonstrate an evolving posterior myocardial infarction in this 44 year old man. Subsequently fulminant congestive heart failure and mitral insufficiency developed. A large posterior left ventricular aneurysm was found at the time of cardiac catheterization, and the electrocardiogram of November 28, 1965 shows T wave inversion in lead V_5.

TABLE II

Coronary Artery Occlusion in 24 Autopsy Cases of Ventricular Aneurysm

Artery	Partial*	Complete
Left anterior descending	11	12
Left circumflex	15	5
Right coronary	14	7

* Partial occlusion was said to be present if more than 50 percent of the lumen was obstructed by plaque.

TABLE III

Commonest Complications Observed in 40 Patients with Ventricular Aneurysm

	Cases	
	no.	% of Total
Congestive heart failure	35	85
Angina	25	64
Rhythm disturbance	16	41
Arterial emboli	2	5

after elective noncardiac operations. One patient had a dissecting aneurysm, and cardiac arrhythmias developed without evidence of an acute myocardial infarction. Four patients died from unrelated causes.

Autopsy: The average diameter of the aneurysm in 27 cases was 5 cm. The outward protrusion from the ventricular wall was difficult to determine, but the thickness of the wall in the center of the aneurysm never exceeded 3 mm. Twelve of the 27 hearts had mural thrombi, whereas only 2 patients had had clinical evidence of systemic embolization. The degree of coronary atherosclerosis was evaluated and the locations and degree of coronary occlusions are shown in Table II. The commonest complications observed are listed in Table III.

Discussion

In the past few years the terms dyskinetic, adynamic and aneurysmal have come into routine use in association with the evaluation of potential operative candidates with coronary artery disease. The use of ventricular angiography and even calculation of ventricular volumes with diagrammatic representation of systolic and diastolic configurations have allowed a more precise estimation of ventricular performance. Yet, the prognostic significance of an aneurysm or large dyskinetic area of the ventricle is not clearly defined.

The 5 year survival rate after initial myocardial infarction has been reported to be as low as 49 percent by Richards et al.[7] and as high as 83 percent by Dimond.[8] Pell and D'Alonzo[9] reported that patients surviving the first 30 days after myocardial infarction had a greater than 12 year life ex-

pectancy. Schlichter et al.[6] stated that life expectancy was reduced by 50 percent if an aneurysm developed after infarction.

In the present study the average length of survival after initial myocardial infarction in patients in whom a ventricular aneurysm developed was 4.8 years, whereas average survival after diagnosis of the aneurysm was 3.9 years. These observations emphasize that development of an aneurysm occurs fairly quickly, usually within 1 year after myocardial infarction, and markedly shortens life expectancy. Whether most dyskinetic areas ultimately develop into actual aneurysms is not within the scope of this study to determine since angiograms were not routinely performed after infarction to identify dyskinetic areas of the ventricle.

Two of the 40 patients (5 percent) had clinical evidence of peripheral embolization. In an autopsy series reported by Dubnow et al.[3] there was a 65 percent incidence of mural thrombi within the aneurysm and a 35 percent incidence of peripheral embolization.

Predisposing factors: Why a ventricular aneurysm develops in some patients after myocardial infarction is a difficult question. It could be theorized that patients with minimal coronary artery disease who have a major myocardial infarction are more prone to development of a large necrotic segment because of the lack of stimulus for development of intercoronary collateral vessels. Certainly, factors such as preexisting hypertension increase the pressure exerted against the ventricular wall supplied by the obstructed coronary artery. Murray[10] demonstrated the immediate development of an expansion chamber in the area supplied by an obstructed coronary in the dog. Simpson et al.[11] observed an immediate dyskinetic segment and reduction in ejection fraction in animals with coronary occlusion. Sequential studies of ventricular volumes obtained from biplane cineangiograms showed a progression in the size of this segment. The postmortem examinations in our series would not support the concept of minimal coronary artery disease since only 3 of 27 patients failed to have extensive coronary arteriosclerosis. In addition, 16 patients were known to have recurrent myocardial infarctions.

Surgical indications: Because of the grave complications of ventricular aneurysms, most investigators[12–18] have emphasized the importance of surgical excision, which has been followed in most instances by a dramatic improvement in cardiac function. The findings of such extensive coronary artery disease emphasize the need to perform coronary arteriography in cases of known ventricular aneurysm since revascularization of coronary vessels not supplying the infarcted area is probably necessary in most instances.

The diagnosis of ventricular aneurysm has usually been made by clinical methods or postmortem examination. The actual necrotic area of the heart wall was relatively small, averaging only 5 cm in diameter although in many instances it protruded outward for a considerable distance. The cardiomegaly routinely seen on chest X-ray film was undoubtedly related in some degree to dilatation or hypertrophy of unaffected ventricle. Experimental studies have emphasized the marked increase in cardiac work caused by small aneurysms containing only a fraction of each stroke volume and the rapid development of cardiac failure as the aneurysm enlarges.[19]

It was significant that no patient in the present study was asymptomatic, and 85 percent were being treated for symptoms of heart failure. This high incidence of cardiac failure should be a guide to the deleterious effects of relatively small dyskinetic areas. The marked degree of coronary atherosclerosis seen in all vessels of the patients with ventricular aneurysm supports the suggestion of Johnson et al.[20] for combining resection of dyskinetic areas with direct myocardial revascularization.

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Coexisting Left Anterior Hemiblock and Inferior Wall Myocardial Infarction

Vectorcardiographic Features

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Using the Frank lead system, the vectorcardiographic features of coexisting left anterior hemiblock and inferior wall myocardial infarction were characterized in 25 patients. The vectorcardiographic findings most useful for the diagnosis of coexisting left anterior hemiblock and inferior myocardial infarction are: Frontal plane: (1) clockwise and superior inscription of the 20 to 30 msec QRS vectors, (2) counterclockwise and delayed inscription of the terminal 40 msec QRS vectors, (3) maximal QRS deflection vector located in the left superior quadrant, and (4) major area of the QRS loop above the X axis. Sagittal plane: (1) superior inscription of the 20 to 30 msec QRS vectors, (2) deviation of the maximal QRS deflection vector superiorly and posteriorly, (3) delay in inscription of the terminal 40 msec QRS vectors, and (4) figure-of-eight or counterclockwise rotation of the QRS loop. Because of the difficulties in the electrocardiographic recognition of coexisting left anterior hemiblock and inferior myocardial infarction, utilization of the Frank vectorcardiogram appears to be a superior means for diagnosis.

The existence of both isolated[1] and transient[2–5] left anterior hemiblock is well established. Electrocardiographic features necessary for the diagnosis of this entity include abnormal left axis deviation, QRS complex duration between 80 and 120 msec with initial r waves in leads II, III, aVF and S waves in leads V_5, V_6.[1] It has been proposed that block of the anterior-superior fascicle of the left bundle branch system cannot be diagnosed electrocardiographically in the presence of inferior wall myocardial infarction.[1,3,6] The latter condition can result in abnormal left axis deviation, on the basis of the presence of large negative Q waves in scalar leads II and III, causing the frontal plane QRS axis to shift to the left and superiorly.[7] In a recent report[8] describing left bundle branch hemiblocks associated with acute myocardial infarction, care was taken not to include cases in which axis deviation was due to the Q wave of infarction.

The vectorcardiographic criteria for isolated left anterior hemiblock have recently been formulated.[9] Briefly, they are counterclockwise rotation of the QRS loop in the frontal plane, initial 20 msec vectors directed inferiorly and to the left or right, mean QRS axis in the frontal plane directed to the left and superiorly and delay of the inscription of the terminal 60 to 100 msec QRS vectors. Furthermore, it has been demonstrated on the basis of

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TABLE I

Group I. Twenty-Five Cases of Combined Left Anterior Hemiblock and Inferior Wall Infarction

Case no.	Age (yr) & Sex	Diagnosis	Electrocardiogram	Chest X-Ray or Other Findings
		A. Patients with a Definite Past History of Myocardial Infarction		
1	60M	CAD	SR, LAHB, RBBB	Normal
2	65M	CAD	1°AVB, LAHB	Left ventricular enlargement
3	70M	CAD	1°AVB, LAHB, ALMI	Left ventricular enlargement
4	75M	CAD	AF, LAHB, RBBB	Left ventricular enlargement
5	60M	CAD, VSD	SR, LAHB, RBBB	Catheterization: VSD, anterolateral dyskinesia, ventricular septal aneurysm, LAD 80%, LC 80%, RC 80%
6	63M	CAD	SR, LAHB	Normal
7	67F	CAD	SR, LAHB	Normal. Postmortem findings: R and L CAD, old inferior wall myocardial infarction
8	71M	CAD	SR, LAHB, RBBB	Normal
9	48M	CAD	SR, LAHB, PWMI	Left ventricular enlargement
10	66M	CAD	SR, LAHB, RBBB, ASMI	Left ventricular enlargement
11	52M	CAD	SR, LAHB, ASMI	Left ventricular enlargement
12	46M	CAD	SR, LAHB, ALMI	Left ventricular enlargement
13	75F	CAD	SR, LAHB, ASMI	Left ventricular enlargement
14	67M	CAD	SR, LAHB	Normal
15	50M	CAD	1°AVB, LAHB, ASMI	Left ventricular enlargement
		B. Patients with Angina Pectoris but No Definite History of Infarction		
16	70M	CAD	1°AVB, LAHB	Left ventricular enlargement
17	48M	CAD	SR, LAHB	Sclerotic aorta. Catheterization: 60% RC
18	57M	CAD	SR, LAHB, ASMI	Left ventricular enlargement
19	75M	CAD	1°AVB, LAHB, RBBB	Normal
20	45M	CAD, RHD, AI	SR, LAHB, ASMI	Left ventricular enlargement
21	70F	CAD	SR, LAHB, PWMI	Left ventricular enlargement
22	79F	CAD	SR, LAHB	Normal
23	70M	CAD	1°AVB, LAHB, ASMI	Left ventricular enlargement
		C. Patients with No Evidence of Coronary Artery Disease		
24	19M	PMD	SR, LAHB	Left ventricular enlargement. Catheterization: depressed left ventricular function
25	24M	Traumatic VSD	SR, LAHB, ALMI	Catheterization: VSD. Operation: anteroseptal and inferior wall lacerations

AF = atrial fibrillation; AI = aortic insufficiency; ALMI = anterolateral myocardial infarction; ASMI = anteroseptal myocardial infarction; CAD = coronary artery disease; 1°AVB = first degree atrioventricular block; L = left; LAD = left anterior descending coronary artery; LAHB = left anterior hemiblock; LC = left circumflex coronary artery; % = percent obstruction of coronary artery; PMD = primary myocardial disease; PWMI = posterior wall myocardial infarction; R = right; RHD = rheumatic heart disease; RBBB = right bundle branch block; RC = right coronary artery; SR = sinus rhythm; VSD = ventricular septal defect.

serial vectorcardiographic study that the direction of the initial 25 msec QRS forces is critical for the diagnosis of inferior myocardial infarction. These early vectors are oriented superiorly and rotate to the left in a clockwise fashion.[10]

Utilizing these vectorcardiographic criteria, it appears that the diagnosis of left anterior hemiblock can be made in the presence of inferior wall infarction. The purpose of this paper is to characterize the vectorcardiographic features of coexisting left anterior hemiblock and inferior myocardial infarction. Transient, isolated left anterior hemiblock occurring during acute inferior myocardial infarction will also be described.

Materials and Methods

The study group consisted of 40 patients. *Group I* comprised 25 subjects with vectorcardiographic features of left anterior hemiblock and initial 25 msec frontal plane QRS forces directed superiorly (Table

TABLE II

Range and Mean Values of the Direction in Degrees of the 10, 20, 30, 40, 50, 60, 70 Msec and of the Maximal QRS Deflection Vector in 25 Patients with Coexisting Left Anterior Hemiblock and Inferior Wall Infarction

QRS Vector (msec)	Frontal Plane	Sagittal Plane	Horizontal Plane
10			
Range	170 to −178	175 to −170	0 to ±180
Mean	171	−17	161
20			
Range	0 to −170	12 to −178	146 to −163
Mean	−86	−82	19
30			
Range	175 to −170	142 to −178	122 to −98
Mean	−30	−126	−6
40			
Range	12 to −148	160 to −175	60 to −135
Mean	−42	−136	−37
50			
Range	16 to −158	154 to −178	45 to −165
Mean	−70	−136	−82
60			
Range	170 to −179	158 to −172	163 to −170
Mean	−134	−124	−121
70			
Range	150 to −176	150 to −163	170 to ±180
Mean	−131	−138	−144
Maximal QRS Vector			
Range	13 to −178	−2 to −175	136 to −132
Mean	−43	−118	−42

TABLE III

Range and Mean Values of the Magnitude in Millivolts of the 10, 20, 30, 40, 50, 60, 70 Msec and of the Maximal QRS Deflection Vector in 25 Patients with Coexisting Left Anterior Hemiblock and Inferior Wall Infarction

QRS Vector (msec)	Frontal Plane	Sagittal Plane	Horizontal Plane
10			
Range	0.033 to 0.160	0.043 to 0.275	0.28 to 0.175
Mean	0.0846	0.110	0.089
20			
Range	0.051 to 0.492	0.037 to 0.800	0.056 to 0.571
Mean	0.195	0.260	0.199
30			
Range	0.051 to 0.968	0.029 to 1.175	0.135 to 1.190
Mean	0.431	0.366	0.496
40			
Range	0.096 to 1.271	0.164 to 1.559	0.090 to 1.333
Mean	0.502	0.514	0.606
50			
Range	0.196 to 1.322	0.200 to 1.779	0.098 to 1.333
Mean	0.446	0.567	0.567
60			
Range	0.094 to 0.936	0.067 to 1.200	0.135 to 1.206
Mean	0.372	0.393	0.440
70			
Range	0.070 to 0.730	0.040 to 0.914	0.045 to 1.014
Mean	0.309	0.290	0.320
Maximal QRS Vector			
Range	0.283 to 1.389	0.397 to 1.898	0.434 to 1.396
Mean	0.686	0.747	0.808

I). Twenty-three patients had clinical evidence of coronary artery disease manifested by symptoms compatible with angina pectoris. There were 19 men and 4 women whose age ranged from 46 to 79 years (mean 63). Sixteen of the 23 (70 percent) had a definite history of previous myocardial infarction. All had electrocardiographic evidence of left anterior hemiblock and 11 (48 percent), infarction patterns (8 anterior and 3 posterior). Six subjects had right bundle branch block. Included in group I were 2 male patients without evidence of coronary artery disease: 1 patient with primary myocardial disease, aged 19 years, and 1, aged 24 years, with traumatic lacerations of the inferolateral and anteroseptal left ventricle.

Group II consisted of 7 patients with acute inferior myocardial infarction and coexisting left anterior hemiblock. Three of the 7 had evidence of old anteroseptal myocardial infarction. All diagnoses were made on the basis of serial electrocardiographic and vectorcardiographic changes which were compatible with acute inferior myocardial infarction. In addition, severe retrosternal chest pain of more than 1 hour's duration and elevated serum enzyme levels [serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK)] present in all cases. In 2 cases, left anterior hemiblock appeared transiently during the early stages of acute infarction.

Group III consisted of 8 patients with clinical, electrocardiographic and vectorcardiographic evidence of acute inferior myocardial infarction and coexisting abnormal frontal plane left axis deviation without the features of left anterior hemiblock. In 3 cases the abnormal left axis deviation was transient.

Vectorcardiograms in the 3 plane projections were recorded with patients in the supine position and use of the Frank lead system.[11] The fourth intercostal space was used for placement of the chest electrodes as suggested by Langner et al.[12] for the supine position. The vectorcardiograms were recorded on a DR-8 Electronics for Medicine light beam oscilloscopic photographic recorder using a vectorcardiographic channel (model VET-6). Still and timed vectorcardiograms (running loops) were taken in the frontal, left sagittal and horizontal planes. The still loops were magnified to provide a better analysis of the initial and terminal components of the QRS loop; this degree of magnification averaged from 50 to 80 mm for ¼ mv. Timed vectorcardiograms were taken at a paper speed of 75 to 100 mm/sec using previously described techniques.[13,14] The loops were interrupted at an interval of 2 msec; the direction of rotation was indicated by a comet with the "tail" pointing in the direction of inscription. The following measurements were made in all vectorcardiograms: (1) direction and magnitude of the 10, 20, 30, 40, 50, 60 and 70 msec QRS vectors

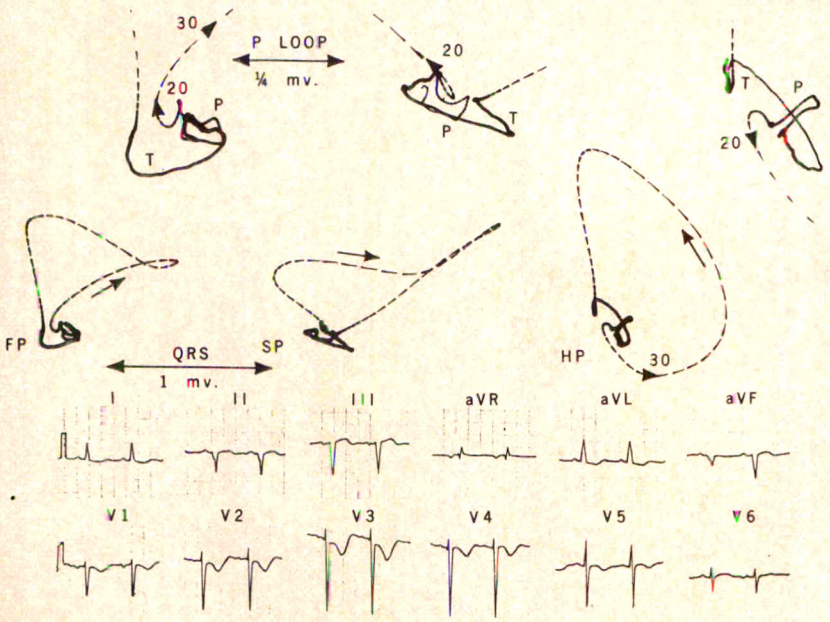

Figure 1. Vectorcardiogram and electrocardiogram of a 67 year old man with coexisting left anterior hemiblock and inferior wall myocardial infarction. Note the clockwise and superior inscription of the initial 40 msec vectors. The loop then rotates counterclockwise in the frontal plane with terminal delay.

in the 3 planes; (2) direction and magnitude of the maximal QRS deflection vector; and (3) rotation of the QRS loop.

These findings were compared to those from a group of 41 patients with isolated left anterior hemiblock.[9]

Results

Group I

The vectorcardiographic data in the 25 cases of coexisting left anterior hemiblock and previous inferior wall infarction are summarized in Tables II and III.

Frontal Plane

Rotation: In all 25 cases the initial 20 to 30 msec QRS vectors rotated in a clockwise fashion (Fig. 1). This initial rotation is different from that of uncomplicated left anterior hemiblock, which results in counterclockwise rotation of these vectors.[9] In all cases the balance of the QRS loop beyond the inscription of the 40 msec vectors rotated counterclockwise, and this reversal in rotation resulted in a figure-of-eight configuration in 14 cases (56 percent). This change in rotation was a constant and characteristic feature. Beyond the inscription of the 40 msec vectors, the rotation was similar to that in uncomplicated left anterior hemiblock.[9] This change in rotation is useful to differentiate coexisting inferior infarction and left anterior hemiblock from isolated inferior infarction, which results in a completely clockwise rotation in the frontal plane.[10]

Duration: The duration of the QRS loop ranged between 80 and 130 msec, and a significant delay in inscription of the terminal (beyond the 60 msec vector) vectors was a constant feature. Only those patients with right bundle branch block had a QRS duration greater than 110 msec.

Direction (Tables II and III): In all 25 cases the 20 to 30 msec vectors were directed superiorly, and in all but 2 cases the 40 msec vector was oriented superiorly. This contrasts with isolated left anterior hemiblock which results in inferiorly directed 20 msec vectors. In 20 patients (80 percent) the 40 msec vectors were directed to the left. Except for the initial 20 msec vectors, the direction was similar to isolated left anterior hemiblock, that is, superior and leftward displacement of the QRS loop (Fig. 2).

Sagittal Plane

Rotation: In 14 of the 25 cases (56 percent) the QRS loop rotated in a figure-of-eight fashion,

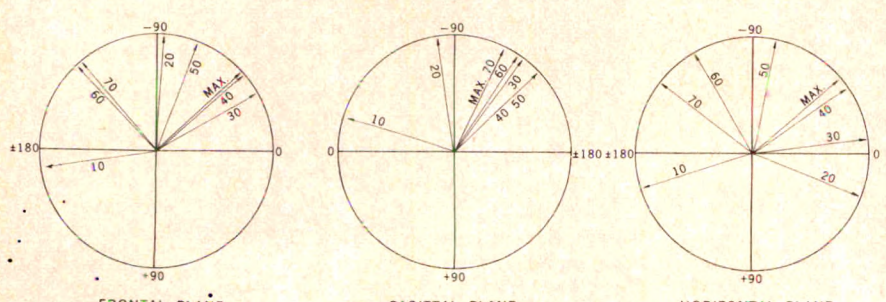

Figure 2. Distribution of the mean 10, 20, 30, 40, 50, 60, 70 msec and maximal QRS deflection vectors in the frontal, left sagittal and horizontal planes from 25 patients with coexisting left anterior hemiblock and inferior wall myocardial infarction.

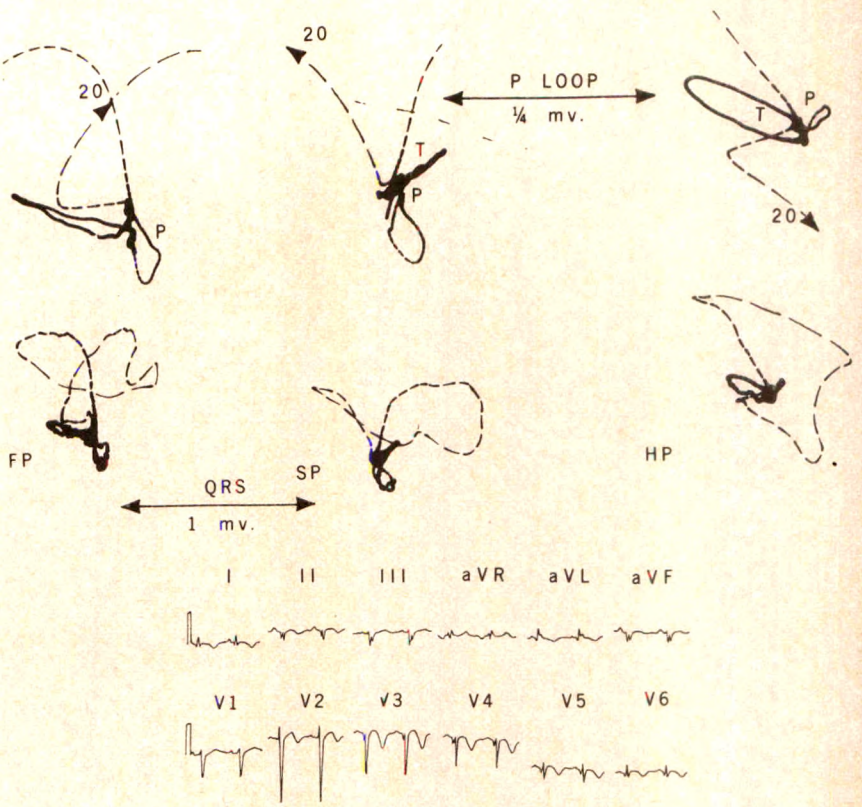

Figure 3. Vectorcardiogram and electrocardiogram of a 24 year old patient with traumatic lacerations of the anteroseptal and inferolateral walls of the left ventricle. Note the superior and clockwise inscription of the initial 20 msec vectors in the frontal plane. The loop then reverses rotation with delayed inscription of the terminal 40 msec vectors.

in 7 the rotation was counterclockwise and in 4 clockwise. In all cases the 20 to 30 msec vectors rotated clockwise. The terminal 40 msec vectors inscribed a delay in all cases. These findings are similar to those of isolated left anterior hemiblock, except that in the latter the initial 20 to 30 msec vectors usually rotate counterclockwise.[9]

Duration: As in the frontal plane, the QRS duration was between 80 and 110 msec for patients without right bundle branch block.

Direction (Tables II and III): The 20 to 30 msec vectors were directed superiorly in all cases, in contrast to isolated left anterior hemiblock, which results in inferiorly directed 20 msec vectors. In the majority of patients (20 of 25 or 80 percent) most of the QRS loop area was displaced superiorly and posteriorly (Fig. 2).

Horizontal Plane

Rotation: Seventeen of 25 cases (68 percent) manifested counterclockwise rotation, 6 figure-of-eight and 2 clockwise. These findings are similar to those described for isolated left anterior hemiblock.[9]

Duration: The duration of the QRS loop was 80 to 110 msec for those patients without right bundle branch block.

Direction (Tables II and III): In 9 of 25 cases (36 percent) the initial 20 msec vectors were directed posteriorly, and in these cases there were significant Q waves of infarction present in the precordial electrocardiographic leads. These results can be contrasted with isolated left anterior hemiblock where only 5 of 41 (12 percent) had these early forces directed posteriorly. Six patients with right bundle branch block showed terminal forces directed to the right and anteriorly.

Clinical features of group I: Compared with isolated left anterior hemiblock, there was a much higher incidence of coronary artery disease and previous history of myocardial infarction. Of interest was a 24 year old patient with stab wounds of the anteroseptal and inferolateral walls of the left ventricle (Fig. 3).

Group II

In all 7 patients with left anterior hemiblock and coexisting acute inferior wall infarction, initial 25 msec QRS vectors developed which rotated clockwise in the frontal plane and were directed superiorly (Fig. 4). Their terminal 40 msec QRS vectors rotated counterclockwise in the same plane with delayed inscription, and the major portion of the QRS loop was in the left superior quadrant. The sagittal plane QRS vectors were similar to those in group I. In all respects the vectorcardiographic characteristics of the QRS loop in these patients were similar to those in group I. In group II there were 4 patients with vectorcardiographic evidence of old myocardial infarction in other sites (3 anterior and 1 posterior). None had right bun-

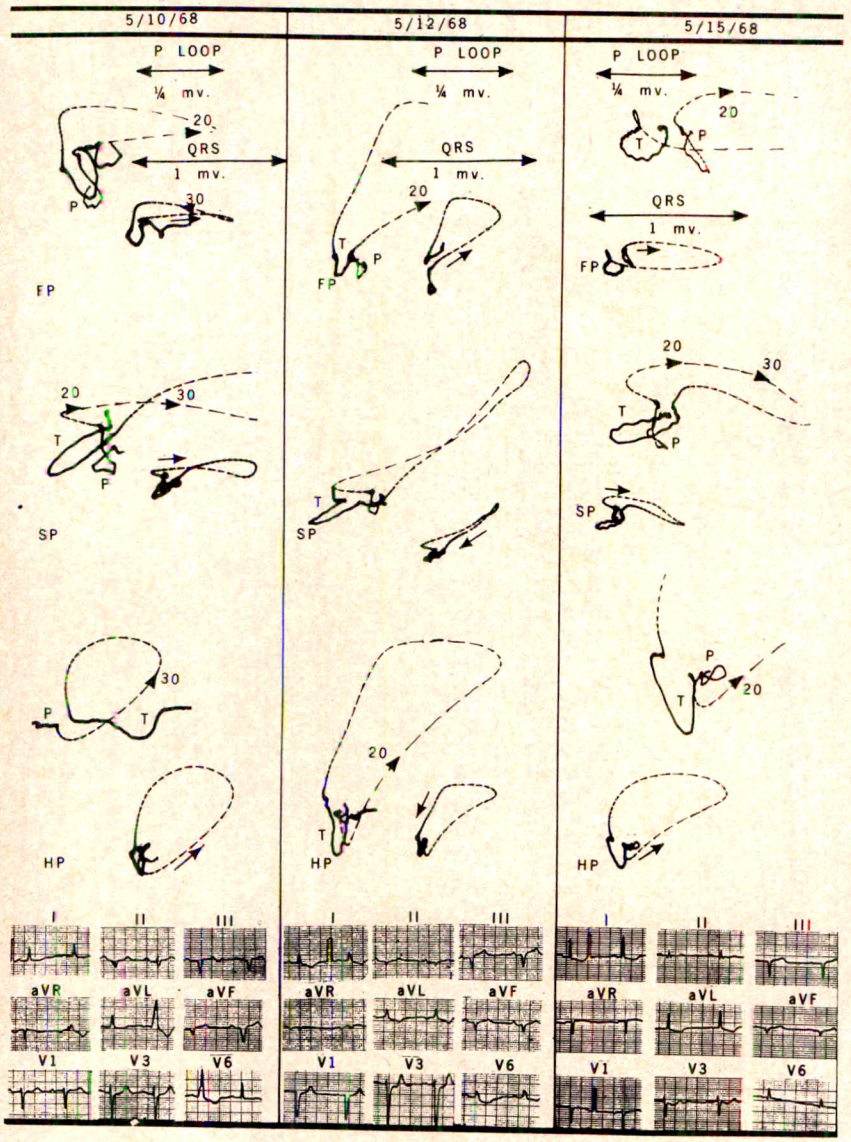

Figure 4. Serial vectorcardiograms and electrocardiograms of a 70 year old patient with acute inferior wall myocardial infarction and transient left anterior hemiblock. On May 10, 1968 the frontal plane QRS loop has a figure-of-eight shape with a duration of 78 msec. On May 12 the entire frontal plane QRS loop rotates counterclockwise except for the initial 20 msec vectors and is directed superiorly. The QRS duration is 100 msec with delayed inscription of the terminal 40 msec vectors. On May 15 the frontal plane QRS loop rotates completely clockwise and is directed inferiorly. The QRS duration is 74 msec.

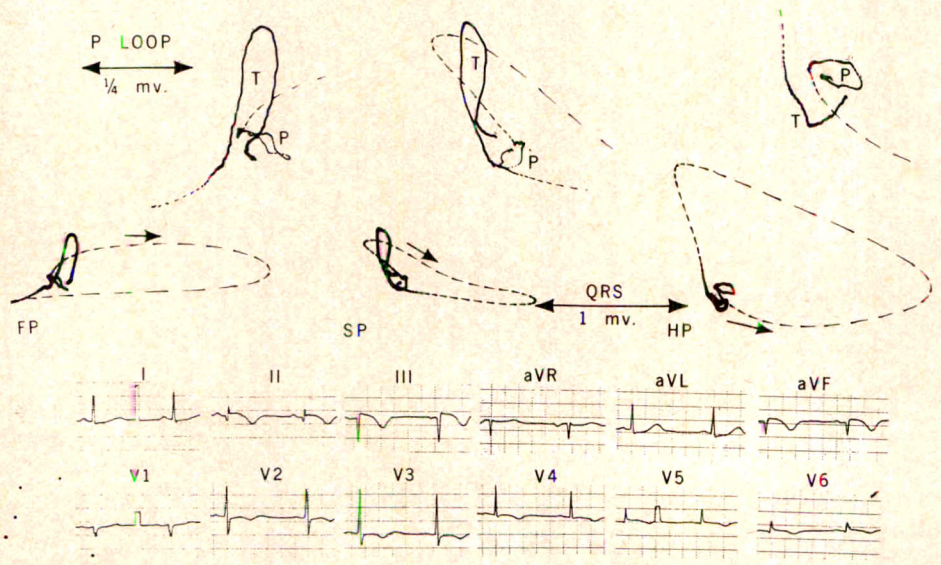

Figure 5. Vectorcardiogram and electrocardiogram from a 37 year old man with acute inferior wall myocardial infarction. Note the frontal plane QRS displacement superiorly and to the left. The entire frontal plane loop rotates clockwise with no delay of inscription of the terminal 40 msec vectors. There is no coexisting left anterior hemiblock.

dle branch block. In the 2 cases in which left anterior hemiblock was transient, the duration of the QRS loop increased up to 20 msec during the episode, and all other transient features were similar to those described above. After disappearance of this conduction defect, the QRS loop diminished in duration with reversion to a pattern not unlike that described for uncomplicated inferior myocardial infarction.[10]

Group III

In 6 of the 8 cases with acute inferior wall infarction and abnormal left axis deviation, the frontal plane QRS loop rotated clockwise (Fig. 5). In the other 2 patients the frontal plane loop was inscribed in a figure-of-eight shape. In all cases the initial 30 msec vectors were directed superiorly, and the major portion of the loop was located in the left superior quadrant. There was no delay of the terminal 40 msec vectors. In the sagittal plane 7 of 8 cases manifested clockwise rotation. A single case showed counterclockwise rotation. Horizontal plane loops were unaltered except in 1 patient with an old anterior wall myocardial infarction. No patient had right bundle branch block. All of these findings were compatible with uncomplicated acute inferior wall infarction.[10] The distinguishing characteristic of the group was a maximum frontal plane QRS vector in the left superior quadrant. In 3 cases the abnormal superior and leftward deviation was transient.

Discussion

On the basis of existing criteria for left anterior hemiblock[9] and inferior wall myocardial infarction,[10,15–17] the simultaneous presence of these 2 abnormalities can be diagnosed utilizing the Frank vectorcardiogram. The validity of the results in group I, with vectorcardiographic features of old inferior infarction and coexisting left anterior hemiblock, is further demonstrated by identical changes in group II during acute inferior infarction. A past history of myocardial infarction in only 70 percent of patients with graphic evidence of this abnormality is not surprising and has been documented in a previous epidemiologic study.[18] Furthermore, the majority of the 30 percent without "prior history" of myocardial infarction had a history compatible with angina pectoris. Traumatic lacerations of the inferior wall of the left ventricle with resulting superiorly directed initial vectors, and anteroseptal laceration with features of left anterior hemiblock in a single patient is of interest, since anteroseptal myocardial infarction is a recognized cause of left anterior hemiblock.[18] This combination of acquired traumatic defects with left anterior hemiblock has not been previously described.

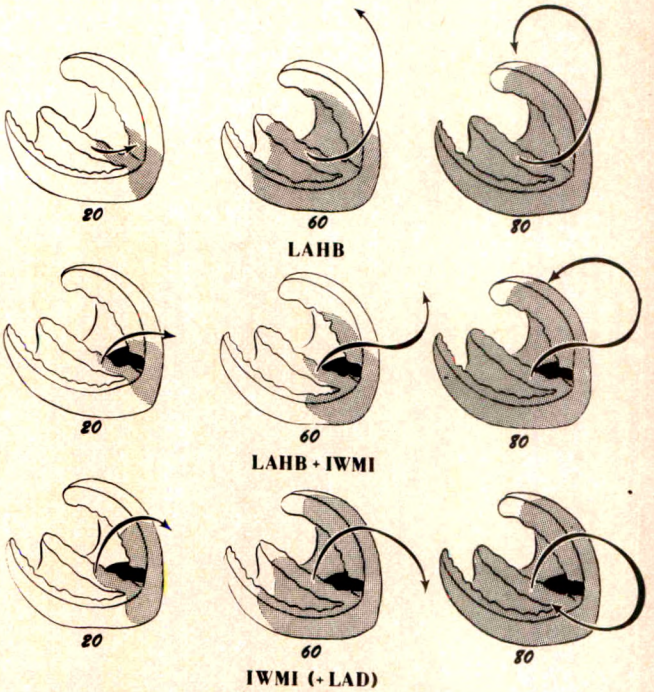

Figure 6. Sequence of ventricular activation in (1) isolated left anterior hemiblock (LAHB), (2) LAHB and inferior wall myocardial infarction, and (3) inferior wall myocardial infarction with left axis deviation (LAD) and no left anterior hemiblock.

In 12 of 30 cases with coronary artery disease, inferior wall infarction, and left anterior hemiblock there was vectorcardiographic evidence of anterior wall infarction, probably indicating the extent of right and left coronary artery disease in this group. The transient occurrence of left anterior hemiblock during acute inferior wall infarction in 2 cases stresses the variability of infarction sites in relation to hemiblock. A single case of isolated left anterior hemiblock with coexisting acute inferior infarction has been reported.[8] It is possible that the injury and myocardial inflammation attendant to inferior infarction extended to the septum or anterior wall, or both, causing this abnormality. The explanation of this unusual phenomenon must await future postmortem correlative study. A patient with primary myocardial disease had vectorcardiographic evidence of coexisting left anterior hemiblock and inferior wall infarction. This is compatible with previously described abnormal QRS vector patterns for primary myocardial disease, presumably based on myocardial fibrosis.[19]

Sequence of ventricular activation: A comparison of the sequence of ventricular activation for isolated left anterior hemiblock, left anterior hemiblock with inferior wall infarction, and inferior wall infarction with abnormal left axis deviation (no hemiblock) is shown in Figure 6. With coexisting left anterior hemiblock and inferior wall infarction, the following sequence occurs. The

usual inferiorly directed initial 20 msec vector of isolated left anterior hemiblock, representing inferior wall activation by way of the intact left posterior-inferior fascicle, is directed superiorly and rotates clockwise due to necrosis of the inferior wall of the myocardium.[10] After inscription of these unbalanced forces, frontal plane activation continues in the usual counterclockwise and leftward fashion owing to late activation of the anterior-superior left ventricle, with delayed inscription of the terminal 40 msec QRS forces. However, the *initial* 10 msec vectors may be directed inferiorly, probably indicating normal septal activation[9] and, although this is still a point of contention,[20] it is important in terms of electrocardiographic recognition of coexisting left anterior hemiblock and inferior wall infarction. Eleven of 25 patients with this vectorcardiographic pattern had initial r waves in scalar electrocardiographic leads II, III and aVF of at least 0.10 mv, thus militating against the diagnosis of inferior infarction. In other patients an embryonic r wave was recorded in these leads. The presence of deep Q waves in leads II, III and aVF, with abnormal left axis deviation as shown from the results in group III, does not necessarily indicate left anterior hemiblock. The vectorcardiogram is, therefore, a superior technique for the diagnosis of coexisting left anterior hemiblock and inferior wall myocardial infarction.

Indeed, the initial 20 msec QRS vectors need not change significantly during transient left anterior hemiblock, thus complicating further the recognition of this conduction defect utilizing standard scalar techniques.[5] The significance of an increase in the scalar QRS duration up to 0.12 second with deep Q waves in leads II and III remains to be studied, and these changes may be suggestive of coexisting left anterior hemiblock and inferior wall infarction. Inferiorly oriented scalar Q waves associated with complete left bundle branch block appear to be specific for coexisting inferior wall infarction.[21]

In summary, the following vectorcardiographic findings appear to be most useful for the diagnosis of coexisting left anterior hemiblock and inferior wall infarction:

Frontal plane: (1) clockwise and superior inscription of the 20 to 30 msec QRS vectors, (2) counterclockwise and delayed inscription of the terminal 40 msec QRS vectors, (3) maximal QRS deflection vector located in the left superior quadrant, and (4) major area of the QRS loop above the X axis.

Sagittal plane: (1) superior inscription of the 20 to 30 msec QRS vectors, (2) deviation of the maximal QRS deflection superiorly and posteriorly, (3) delay in inscription of the terminal 40 msec QRS vectors, and (4) figure-of-eight or counterclockwise rotation of the QRS loop.

Acknowledgments

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Myocardial Lesions in Idiopathic and Alcoholic Cardiomyopathy

Study by Ventricular Septal Biopsy

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Myocardial biopsy specimens from 20 patients with cardiomyopathy were examined by electron and light microscopy. In 11 of 12 patients with idiopathic cardiomyopathy, loss of contractile elements and closely related sarcoplasmic reticulum was seen. Glycogen increase was common. Structural damage of mitochondria was inconsistently present in 5 patients. Examination revealed normal myocardium in 1 patient. In all 8 patients with alcoholic cardiomyopathy, loss of contractile elements and sarcoplasmic reticulum was present. In 5 alcoholic subjects, generalized dilatation of the sarcoplasmic reticulum was a prominent abnormality and in areas of some myofibers was the only structural abnormality. Glycogen increase was common. Mitochondria were structurally normal in 7 patients.

Contractile element-sarcoplasmic reticulum disorganization and loss was a consistent ultrastructural abnormality common to both idiopathic and alcoholic cardiomyopathy. This change, whether secondary or primary, represented the major ultrastructural lesion correlating with myocardial dysfunction in our patients. Generalized swelling of the sarcoplasmic reticulum without disorganization appears to be an early manifestation of myocardial damage in alcoholic cardiomyopathy. Similar change was focal and inconsistent in idiopathic cardiomyopathy. This represented the only consistent difference noted in comparing the 2 groups of patients. Structural damage of mitochondria did not appear to be a major lesion in either idiopathic or alcoholic cardiomyopathy; however, in both conditions mitochondrial numbers were decreased in extensively damaged myofibers. Microtubules were identified in human myocardium and were most commonly observed in areas of contractile element-sarcoplasmic reticulum damage.

Although increasing attention has been directed to the investigation of cardiomyopathy,[1-3] ultrastructural alterations of the myocardium in these disorders are incompletely described. The present lack of such information is in part due to difficulty in safely performing adequate myocardial biopsies and to problems in accomplishing valid electron microscopic examination of small myocardial biopsy specimens.

Electron microscopic study of the myocardium has been described in patients with alcoholic cardiomyopathy[4,5] and in an uncommon variant of heart muscle disease, hypertrophic subaortic stenosis.[6] Similar study of nonalcoholic patients with idiopathic cardiomyopathy is restricted to an occasional case report.[7,8]

This report describes electron and light microscopic changes detected in myocardial biopsies of 20 patients with a diagnosis of cardiomyopathy. Twelve patients had idiopathic cardiomyopathy,

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and 8 had alcoholism. Ultrastructural lesions in the idiopathic and alcoholic patient groups are contrasted; these findings are further compared to those previously reported in alcoholic cardiomyopathy.

Materials and Methods

Patients

All patients were diagnosed as having cardiomyopathy by clinical evaluation in the hospital including cardiac catheterization. Guidelines used for exclusion of other forms of heart disease were similar to those previously reported.[9] Particular care was directed to the exclusion of coronary heart disease. The presence of any of the following excluded the patient from the study group: history suggestive of angina pectoris or myocardial infarction, electrocardiographic evidence of myocardial infarction, elevated blood glucose level, serum lipid abnormality or sustained blood pressures greater than 150 mm Hg systolic or 90 mm Hg diastolic. Serum electrolytes (including potassium and sodium) were normal at the time of study. All but 2 patients were taking digitalis; none had evidence of digitalis overdosage. Clinical findings due to cardiomyopathy have been extensively described,[1–3] and only those patients with clinical findings of unusual interest will be discussed herein. The patients were divided into 2 clinical groups: idiopathic cardiomyopathy (12 patients) and alcoholic cardiomyopathy (8 patients).

Idiopathic cardiomyopathy (Table IA): Twelve patients fulfilled clinical criteria for idiopathic cardiomyopathy. These patients first presented with symptoms and signs of congestive heart failure, primarily left, and generalized cardiac enlargement. Their average age was 37 years (range 20 to 51 years). None had a history of chronic dietary deficiency or had taken medications reported to cause myocardial damage. Clinical features present in 3 patients are briefly described.

A 48 year old white man (Patient 10) presented with congestive heart failure. Other findings included focal areas of pericardial calcification, hepatomegaly, splenomegaly, leukopenia and thrombocytopenia. Cardiac catheterization revealed hemodynamic changes consistent with constrictive pericarditis or restrictive cardiomyopathy. A thoracotomy was performed, and no evidence of pericardial constriction was present.

Only 1 patient, a 45 year old man, had a family history of unexplained heart disease (Patient 11). His 30 year old sister was hospitalized for unexplained cardiac arrhythmia and died suddenly and unexpectedly with documented ventricular fibrillation. A young son has a history of rapid heart action. In this patient symptoms of congestive failure developed in the mid 1950's. In June 1965 he had syncopal episodes associated with a high degree of atrioventricular block. This was treated by long-term pacing of the demand type. Myocardial biopsy was performed in December 1969.

A 21 year old woman (Patient 12) first experienced symptoms of congestive failure in the immediate postpartum period. Cardiac catheterization and myocardial biopsy were accomplished 1 year later when she was asymptomatic and heart size had returned to normal.

Alcoholic cardiomyopathy (Table IB): Seven of the 8 patients drank whiskey or wine, and 1 was a beer drinker. The minimal daily intake recorded was 8 ounces of whiskey or its equivalent. Most drank much more than this and all had been drinkers for many years. The beer drinker had consumed an average of 96 oz daily for 20 years and had drunk the same brand since 1959. Information received from the brewery indicated that cobaltous salts or other unusual additives were not present in this particular beer. Although the

TABLE I

Results of Myocardial Biopsy

Case no.	Age (yr) & Sex	Duration of Symptoms (mo)	Electron Microscopic Findings
		A. Idiopathic Cardiomyopathy	
1	40F	18	Patients 1 to 5: Loss of contractile elements-sarcoplasmic reticulum predominant lesion. Mitochondrial abnormality present but inconsistent. Mitochondrial numbers decreased in areas of damage. Glycogen increase common
2	20M	1	
3	39F	3	
4	47M	3½	
5	33M	3	
6	31F	23	Patients 6 to 11: Loss of contractile elements-sarcoplasmic reticulum and glycogen increase only consistent lesion. The majority of mitochondria were structurally normal but frequently decreased in areas of damage
7	22F	30	
8	51F	8	
9	50M	4 yr	
10	48M	12 yr	
11	45M	15 yr	
12*	21F	12	Normal myocardium
		B. Alcoholic Cardiomyopathy	
13	41M	3	Patients 13–17: Dilatation of sarcoplasmic reticulum the prominent lesion. Contractile element-sarcoplasmic reticulum loss, focal glycogen increase also present. The majority of mitochondria were structurally normal but frequently decreased in areas of damage
14	36M	3–5 wk	
15	38M	7 yr	
16	43M	9	
17	49M	2	
18	47M	18	Patients 18 and 19: Contractile element-sarcoplasmic reticulum loss, glycogen increase. The majority of mitochondria were structurally normal but frequently decreased in areas of damage
19	49M	2	
20	36M	4	Patient 20: Loss of contractile elements; enlarged, glycogen-filled mitochondria.

* Severe heart failure developed 1 week after an uncomplicated pregnancy and delivery. No clinical heart disease was observed 12 months later at the time of biopsy.

diet of the alcoholic subjects varied and was at times inadequate, evidence of chronic dietary deficiency was not present. The clinical findings in these patients were generally similar to those of the patients with idiopathic cardiomyopathy. Their average age was 42 years (range 36 to 49 years).

Methods

Right heart catheterization was carried out in all patients; 3 patients underwent both right and left heart catheterization. Immediately after these procedures, intracardiac needle biopsy of the ventricular septum was performed using a technique previously described.[10] The only significant complication encountered was the development of persistent right bundle branch block in 1 patient, and transient right bundle branch block in another. There has been no detectable clinical difficulty due to these complications.

Myocardial biopsy specimens averaged 1.5 cm in length and 1 to 1.5 mm in diameter. Observations made during development of the procedure indicate that the major part of the biopsy specimen is taken from the muscular septum forming the anteromedial wall of the left ventricle. The technique used and specimens obtained thereby differ from endomyocardial catheter biopsy as described by Konno and Sakakibara.[11]

Electron microscopy: Specimens were immediately fixed for 2 hours with 3 or 4 percent glutaraldehyde in 0.1 M phosphate buffer, ph 7.4. Tissues were then postfixed with 1 percent osmium tetroxide in 0.1 M phosphate buffer. Dehydration was accomplished with increasing concentrations of alcohol and the tissue embedded in an araldite-epon mixture. Blocks were thin-sectioned with diamond knives (DuPont), and sections were stained on uncoated copper grids with uranyl acetate and lead citrate. Electron micrographs were taken with an RCA 3F electron microscope.

Light microscopy: Sections of approximately 1μ thickness were cut from blocks embedded for electron microscopy and stained with toluidine blue or paragon. These were examined for artifact and orientation. Other tissues were processed in the usual manner and stained with hematoxylin and eosin.

Control myocardium: Myocardial biopsy specimens were taken from normal dogs using the same biopsy technique as in man. Identical fixation, embedding, staining and sectioning techniques were used for electron microscopic examination. Grids were scanned and photographed by the same persons examining the human specimens.

Results

Hemodynamic study: At the time of biopsy, resting intracardiac pressure levels were abnormally elevated in 10 patients, high normal to slightly elevated in 8 and normal in 2. Except for the 1 patient with normal myocardium (Case 12) no apparent difference in electron microscopic findings was noted between patients with abnormal and normal resting pressures. Since hemodynamic measurements and cardiac output determinations before and after stress were not routinely performed, the data are considered inadequate for accurate correlation with myocardial morphologic features.

Myocardial ultrastructure: Standard terminology is used in describing myocardial ultrastructure; however, some comment regarding the term *myofibril* is warranted. Fawcett and McNutt[12] have recently shown that, in myocardial fibers, the myofilaments are arranged in a single coherent bundle which is partially subdivided into interconnecting myofilament fascicles (myofibrils) of various diameters. This arrangement differs from fast-acting skeletal muscle in which the contractile material is divided into completely separate myofilament fascicles(myofibrils) of rather uniform diameter. In this text the term myofibrils is used in the context of Fawcett's description.

The results of biopsy in idiopathic and alcoholic cardiomyopathy are described separately. Findings are summarized in Table I. A detailed description follows:

Idiopathic Cardiomyopathy

Myocardial biopsies revealed pathologic change in 11 patients and normal myocardium in 1.

Contractile elements and sarcoplasmic reticulum: Loss and disorganization of contractile elements (myofibrils) and closely related sarcoplasmic reticulum was the only consistent change noted and was present in all 11 biopsy specimens showing abnormality (Fig. 1A to 1C). This change appeared to involve the majority of myocytes observed. The extent of damage ranged from minimal and focal involvement to loss of virtually all of the contractile material within the myofibers. Glycogen was usually increased in such areas, sometimes to a marked degree. The site of beginning pathologic change was uncertain; all bands of the sarcomeres appeared to be involved. In many areas of minimal damage, involvement appeared to begin at the outermost border of the myofibrils at or near the site of closest contact with the investing sarcoplasmic reticulum.

Swelling of the sarcoplasmic reticulum was occasionally observed, but in the idiopathic group this finding was focal and inconsistent. In the absence of swelling, abnormality of the sarcoplasmic reticulum is difficult to assess. However, when contractile element loss was present, close observation revealed disorganization, fragmentation and loss of these tubules.

Mitochondria: Structural abnormality of mitochondria was present in 5 patients (Cases 1 to 5). This consisted of partial to essentially complete loss of cristae mitochondriales with the limiting membrane usually remaining intact (Fig. 2). Swelling was occasionally observed. Mitochondrial change varied markedly in different areas of the same biopsy specimens and was a prominent finding only in an occasional tissue block. Mitochon-

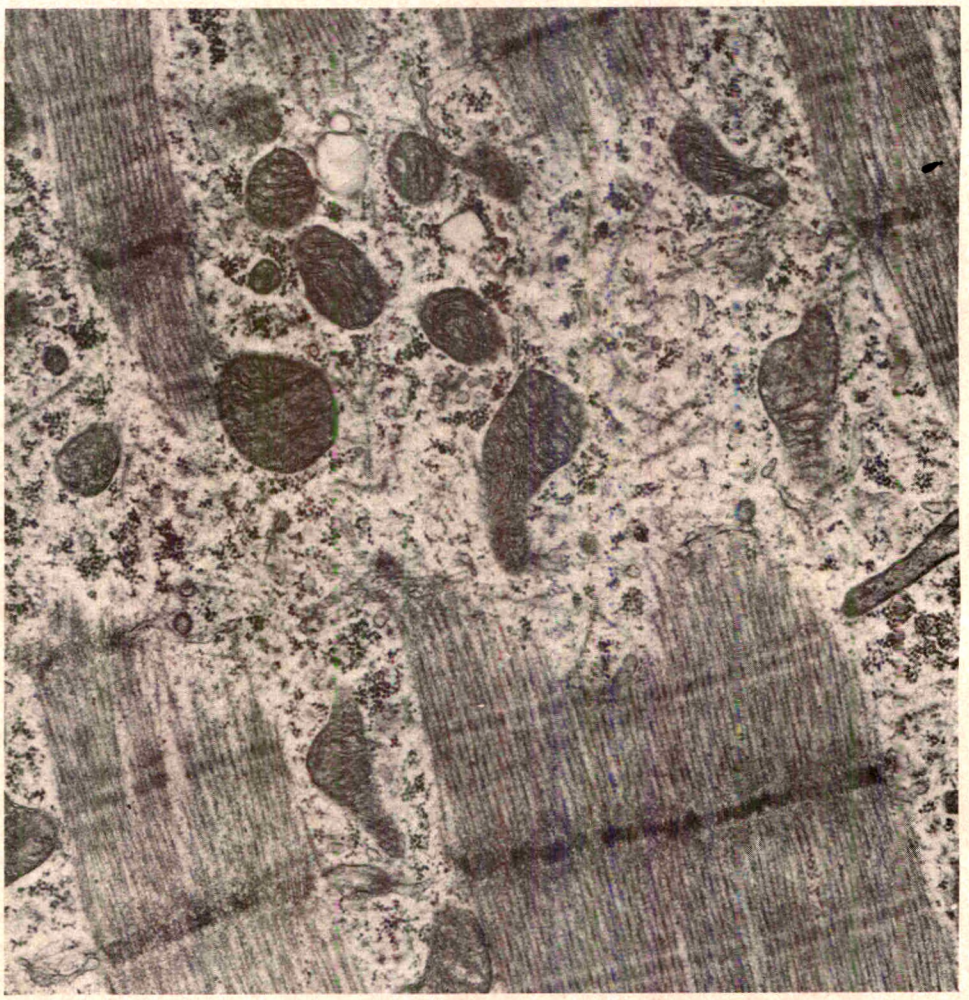

Figure 1A. Idiopathic cardiomyopathy, minimal myofiber damage. There is focal contractile element damage with disorganization and loss of myofilaments. Most mitochondria are structurally intact. Glycogen is present in clumps and appears to be slightly increased. (× 28,500, reduced by 14 percent.)

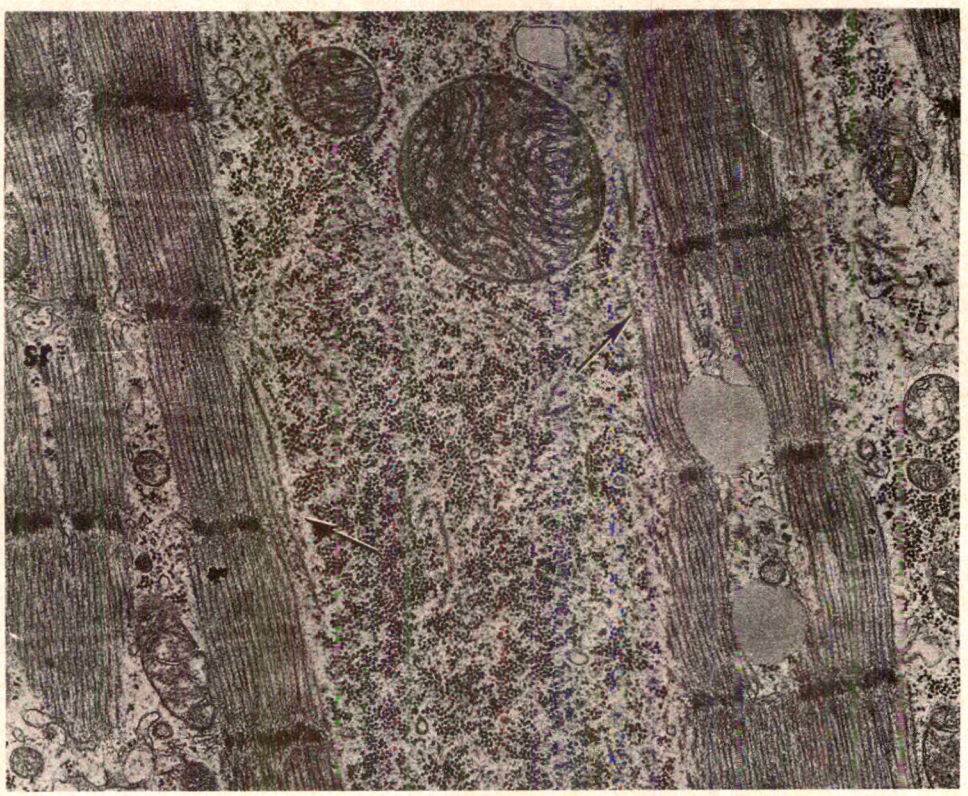

Figure 1B. Idiopathic cardiomyopathy, moderate myofiber damage. There are disorganization and loss of contractile elements with replacement by a large mass of glycogen. Tubules of the sarcoplasmic reticulum are virtually absent along borders of damaged myofibrils (**arrows**) but are readily visible in undamaged areas (sr). Mitochondrial numbers are decreased. A large, oval-shaped but otherwise intact mitochondrion is seen at the top of the micrograph. (× 26,400, reduced by 26 percent.)

Figure 1C. Idiopathic cardiomyopathy, severe myofiber damage. This myofiber shows extensive loss of contractile elements and sarcoplasmic reticulum involving almost its entire transverse diameter. The sarcolemma remains intact along with a small amount of subjacent contractile material at the upper and lower cell borders. Mitochondria are numerous and vary markedly in size and shape. Cristae appear thickened and indistinct; the limiting membrane of many mitochondria is lost. These changes are believed to represent varying stages of mitochondrial degeneration. A mass of glycogen is visible; vacuoles and myelin figures are present. (× 18,900, reduced by 31 percent.)

drial damage was thus inconsistent as compared to other lesions noted.

Although the majority of mitochondria were structurally normal, in areas of extensive contractile element-sarcoplasmic reticulum loss these organelles usually were decreased in number, sometimes to a marked degree (see Fig. 1B and 4). Their location in such areas appeared to be that of random distribution rather than the usual rows between myofibrils.

Light and electron microscopic examination revealed normal myocardium in 1 patient who had recovered from postpartum cardiomyopathy (Case 12).

Alcoholic Cardiomyopathy

Electron microscopic examination of myocardial biopsies revealed pathologic change in all 8 patients (Cases 13 to 20).

Contractile elements: Loss of contractile elements and closely related sarcoplasmic reticulum with or without glycogen increase was present to some degree in all patients (Fig. 3 and 4). This was the only abnormality observed in 2 patients and was similar in detail to that described in the idiopathic group.

Sarcoplasmic reticulum: Generalized dilatation of the sarcoplasmic reticulum with or without disorganization of this tubular network was a prominent finding in 5 patients (Cases 13 to 17). This change was commonly present in areas of myofibers where all other organelles, including contractile elements, appeared structurally normal (Fig. 5).

Mitochondria: The great majority of mitochondria appeared structurally normal in 7 patients. As in the idiopathic patient group, mitochondria were decreased in number in areas of contractile element-sarcoplasmic reticulum loss (Fig. 3). In 1 patient (Case 20) the only beer drinker in the series, markedly enlarged mitochondria containing large amounts of glycogen in the aggregated or alpha form were observed. Findings in this patient have been reported separately.[13] Similar abnormality was not observed in the other alcoholic patients or the idiopathic group.

Other Observations

The following observations apply to both the idiopathic and alcoholic patient groups.

Mitochondria: The distribution and numbers of myocardial mitochondria in cardiomyopathy and

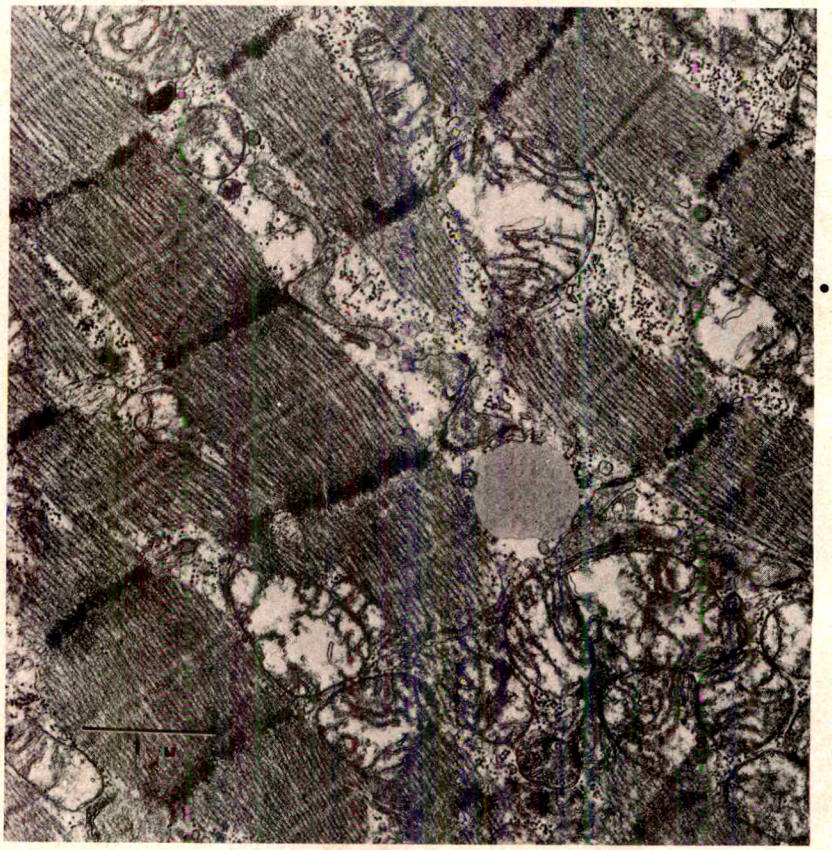

Figure 2. Idiopathic cardiomyopathy, mitochondrial damage. There is disorganization and severe loss of cristae mitochondriales with some mitochondrial swelling. Segments of the limiting membrane appear indistinct in some mitochondria. Contractile elements and sarcoplasmic reticulum appear normal. Glycogen is present in usual amounts. (× 26,400, reduced by 32 percent.)

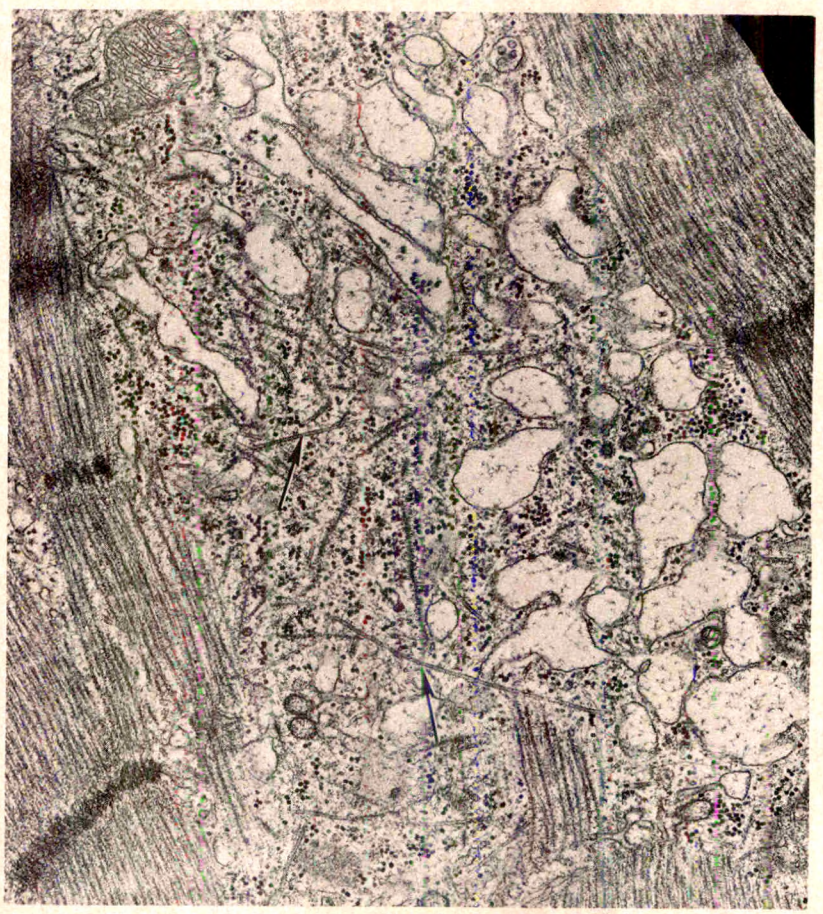

Figure 3. Alcoholic cardiomyopathy. Tubules of the sarcoplasmic reticulum are markedly dilated and there is loss of contractile elements. A number of microtubules are present in the area of damage (**arrows**). Structures resembling myosin filaments are also seen. Mitochondria are essentially absent. (× 35,200, reduced by 28 percent.)

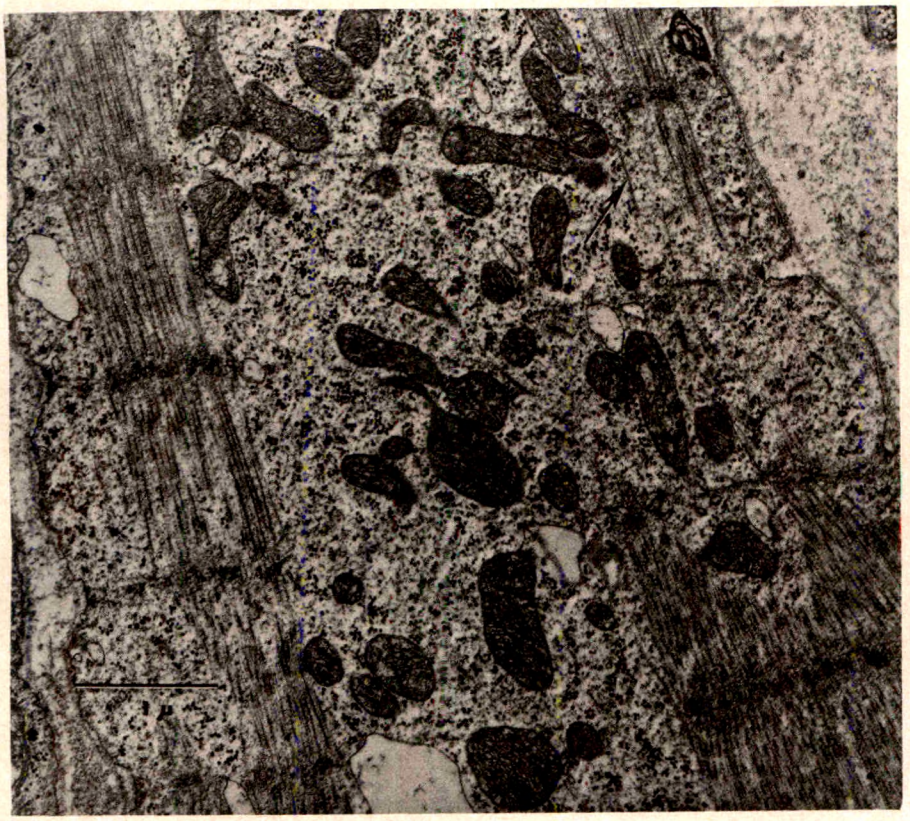

Figure 4. Alcoholic cardiomyopathy. This myofiber shows a marked deficit of contractile elements and sarcoplasmic reticulum. Mitochondria are randomly distributed and vary in shape; however, most appear to be intact. Microtubules are present (**arrows**). A myelin figure and several clear vesicles are seen. The sarcolemma is intact. (× 27,500, reduced by 34 percent.)

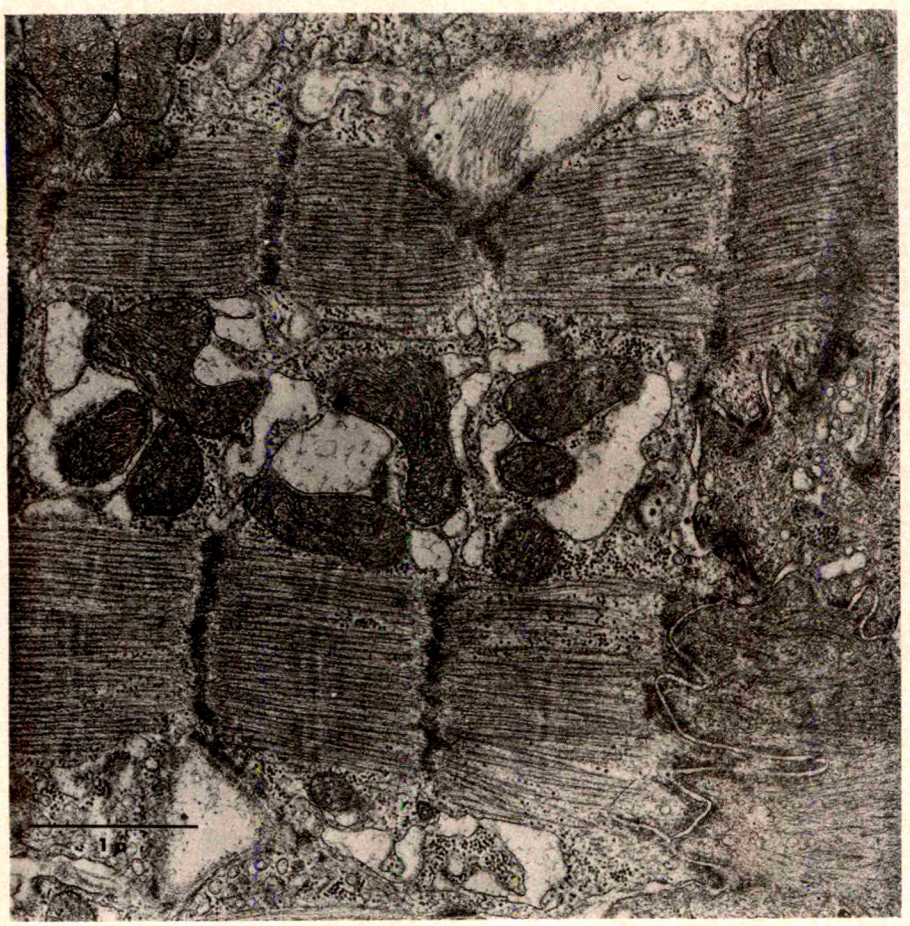

Figure 5. Alcoholic cardiomyopathy. There is marked dilatation of the sarcoplasmic reticulum and also T tubules. Mitochondria and sarcomeres appear normal except for apparent compression by dilated tubules of the sarcoplasmic reticulum. An intercalated disc on the right is generally normal except for focal widening (w) where the disc is in close proximity to dilated tubules. (× 35,200, reduced by 37 percent.)

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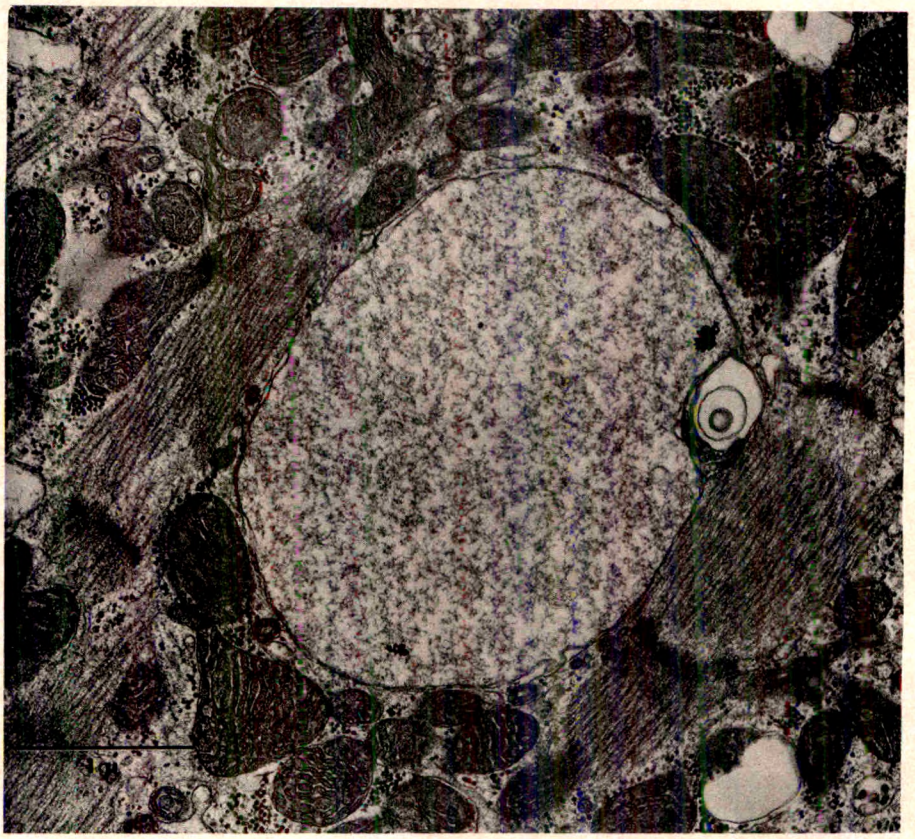

Figure 6. Large membrane-enclosed vesicles as shown in this micrograph were occasionally observed in both idiopathic and alcoholic cardiomyopathy. These contained unstructured material and were less dense than the surrounding subcellular components. The extremely dense material within the vesicle is precipitated lead stain. (× 35,200, reduced by 33 percent.)

in normal myocardium were compared. Focal groupings or aggregations of mitochondria were observed in both. These mitochondrial groupings were almost invariably located in areas showing severe focal contracture or compression of the myofibers as evidenced by distances between Z lines of 1 μ or less and marked scalloping of the sarcolemma. The apparent effect of contracture is to compress areas of the cell and force mitochondria into pockets or groups of variable size and shape. The changes described are believed to be induced by the biopsy procedure and by handling of viable myocardial specimens. When contracture was absent, the distribution of mitochondria in cardiomyopathy usually was similar to that of normal myocardium.[12,14]

Glycogen: The monoparticulate or beta form of glycogen usually present in heart muscle was commonly increased in damaged myofibers of both patient groups. This increase was observed only in the presence of contractile element-sarcoplasmic reticulum damage (Fig. 1B).

Nuclei: No consistent abnormality of myocardial nuclei was observed. However, no attempt was made to interpret minimal variations in the staining pattern and distribution of nuclear chromatin. In 1 alcoholic patient, a small percent of myocardial nuclei contained clusters of particulate material. The particles were rounded, stained densely with lead citrate and measured 20 to 30 mμ in diameter. Although not conclusively identified, the particles were identical in size, shape and staining characteristics to cytoplasmic glycogen.

Sarcolemma: The basement and plasma membrane layers of the sarcolemma usually appeared structurally intact even in areas of damage.

Intracellular inclusions: Lysosomes were consistently increased in damaged cells as compared to normal. Lipofucsin pigment was abundant and appeared to be increased in some specimens. Intracellular lipid was present but did not appear increased in any specimens examined.

Microtubules: Frequently, in areas of contractile element damage, relatively straight, thin, nonbranching tubules were present which resembled neither sarcoplasmic reticulum or myofilaments (Fig. 3). The tubules were of indeterminate length and measured approximately 25 mμ in diameter. Their outer walls were dense, and the center was of low density. Morphologically these structures were similar to microtubules as described by Ledbetter and Porter.[15] Similar structures were seen in normal control myocardium but were comparatively uncommon.

Vesicles: Large vesicles were observed within a small percent of damaged myofibers in 7 cases, both idiopathic and alcoholic (Fig. 6). These structures varied in size and shape with diameters ranging from 1.5 to 15 μ. Some were surrounded by a double membrane; others did not appear to be completely enclosed. The vesicles were less dense than the surrounding subcellular components but

did contain some unstructured material and at times small amounts of glycogen. Despite their size, there was no evidence of compression of adjacent organelles. These vesicles appeared similar to those described by Hibbs et al.[4] in patients with alcoholic cardiomyopathy.

Interstitial space: Interstitial fibrous tissue was commonly increased. Capillaries appeared normal. The small arteries present appeared normal. However, examination of adequate numbers of small vessels requires serial sectioning of the biopsy specimen for light microscopic examination and this was rarely done. Inflammatory cells were absent.

Discussion

Comparison and significance of ultrastructural changes: Combined loss of contractile elements and the closely surrounding sarcoplasmic reticulum with glycogen increase was the most common ultrastructural abnormality in both idiopathic and alcoholic cardiomyopathy. These changes were indistinguishable in the 2 groups. Presently too few patients have been studied to determine whether contractile element-sarcoplasmic reticulum loss is an initial and progressive lesion or a secondary one with earlier lesions having disappeared or gone undetected. Whatever the case, the prevalence of this finding in cardiomyopathy suggests that a large percent of viable myofibers have impairment of contractile function due to loss and disorganization of the contractile elements and sarcoplasmic reticulum. Although other factors undoubtedly play a role, these changes are believed to represent the major ultrastructural lesion associated with chronic myocardial dysfunction in our patients with idiopathic and alcoholic cardiomyopathy. Alexander,[5] in previous work on alcoholic cardiomyopathy, believed that loss of contractile elements was a major lesion contributing to cardiac dysfunction in his patients.

Generalized dilatation of the sarcoplasmic reticulum with or without change of other subcellular structures was commonly observed in the alcoholic patients. In the idiopathic group similar change of the sarcoplasmic reticulum was focal and was not present as the only abnormality. This was the only notable difference between the 2 groups.

Dilatation of the sarcoplasmic reticulum without other structural abnormality is an unusual lesion. Electron microscopic examination of skeletal muscle in patients with alcoholic myopathy[16] revealed destruction of myofilaments and mitochondria; no isolated change of the sarcoplasmic reticulum was reported. However, in studies of rats fed alcohol,[17] dilatation of the smooth and rough endoplasmic reticulum of the liver has been reported to be the earliest change. Lindbaugh and Lieber[18] reported that dilated endoplasmic reticulum was a major ultrastructural abnormality detected in the intestinal mucosa of 1 patient with alcohol-induced malabsorption of vitamin B_{12}. These findings suggest that alcohol can produce changes of the endoplasmic reticulum in other tissues; however, the relation of such changes to myocardial lesions in our alcoholic patients is not clear. In the heart, the complex function of this system of tubules regarding impulse conduction and electromechanical coupling points to the sarcoplasmic reticulum as a likely and sensitive site of involvement by lesions initiating myocardial dysfunction. Our observations suggest that swelling of the sarcoplasmic reticulum without apparent disruption is a major and early manifestation of myocardial damage produced by alcohol.

Since the majority of mitochondria were structurally intact, the significance of the inconsistent structural abnormality of mitochondria noted in 5 patients of the idiopathic group is difficult to determine. Mitochondria are susceptible to damage by a variety of conditions including fixation artifact. There was no evidence of complicating states (myocardial ischemia,[19] taking of toxic medications,[20] hypokalemia[21] or other electrolyte abnormality) which are reported to cause mitochondrial damage. The observation of intact mitochondria dispersed throughout areas of contractile element-sarcoplasmic reticulum loss in both groups of patients was an unexpected finding. In such areas the number of mitochondria usually appeared to be decreased; sometimes to a marked degree. This problem deserves more study since precise measurements of the total mitochondrial mass were not made. The findings suggest that mitochondrial loss eventually occurs in both idiopathic and alcoholic cardiomyopathy but may not be a primary lesion in either.

Focal and sometimes generalized increase of glycogen in damaged myofibers of patients with both idiopathic and alcoholic cardiomyopathy was consistently observed. Since glucose-6-phosphatase is not normally present in heart muscle, glucose-6-phosphate cannot be dephosphorylated to glucose and reenter the blood. Glycogen stores are depleted only by entering metabolic pathways within the cell. In cardiomyopathy, glycogen increase in damaged myocytes suggests that enzyme systems necessary for glycogen formation remain intact at a time when glycogen utilization (anaerobic glycolysis) is impaired. The location of the glycolytic enzymes is believed to be either free in the sarcoplasm or loosely bound to the sarcoplasmic reticulum.[22] Although the reason for glycogen increase is unknown, the presence of this finding only in areas of contractile element-sarcoplasmic reticulum damage suggests that these events are related.

Microtubules: These structures are temporary or permanent components of cytoplasm and have been identified in a wide variety of plant and animal cells.[15,23,24] They have been detected in the

myocardium of ferrets,[25] but similar observations in man have not been reported. The function of microtubules is uncertain but may vary according to cell type and with intracellular location. Postulates regarding function include: association with movement of cytoplasm,[15] a cytoskeletal purpose[24] and modification into fibrils of cilia or thick filaments of striated muscle.[24,26] The function of microtubules in areas of contractile element loss in our patients is unknown and needs further study.

Comparison with previous studies: Earlier ultrastructural studies of alcoholic cardiomyopathy have described diffuse myocardial abnormality involving mitochondria, contractile elements and to some extent the sarcoplasmic reticulum.[4,5] Findings in our alcoholic patients differed in that mitochondria were usually normal and the sarcoplasmic reticulum frequently showed striking and isolated change. The reason for these differences is not clear; accurate comparison of our patients and methods with those previously reported may not be possible.

Abnormally increased numbers of myocardial mitochondria in large aggregations (mitochondriosis) have been reported in alcoholic cardiomyopathy,[5] hypertrophic subaortic stenosis[6] and vitamin B_1 deficiency.[27] Such random groupings of mitochondria were present to some degree in most of our human biopsy specimens but were also observed in normal control myocardium. In our material this finding was considered to be largely secondary to contracture and compression of viable myofibers produced by the biopsy technique. When contracture was absent there appeared to be little difference in the number and distribution of mitochondria in cardiomyopathy and normal myocardium.

Recently English workers in light microscopic study of idiopathic cardiomyopathy[28] described unusual structures within myocardial fibers which were termed "mark bodies." They suggested that these were living structures of an infectious nature. In their study myocardial biopsy specimens were taken by using a small high speed drill device. Marked contracture is frequent in small specimens and mitochondrial aggregations of variable size and shape are numerous. Mitochondria comprising these groupings may have a normal appearance or show structural change. It seems possible that such mitochondrial aggregations are synonymous with the mark bodies previously described. Other than this possibility, no electron microscopic correlate of such structures was observed in our patients.

Clinical implications: This report is intended to describe the major and consistent ultrastructural lesions of the myocardium in patients with clinically advanced cardiomyopathy. Identification and study of patients before development of marked cardiomegaly and failure should be of value in detecting early ultrastructural lesions.

No information is presently available correlating biochemical and cytochemical study with the observed ultrastructural lesions in our patients. Such correlation is necessary before the role of morphologic lesions in myocardial dysfunction can begin to be determined. Accurate identification of structural lesions restricted to or predominantly involving specific subcellular organelles should provide guidance in selecting specific biochemical and cytochemical assays.

Pathologic change of the myocardium in this group of patients was readily detected by biopsy of the ventricular septum. Considering the diffuseness of myocardial involvement in cardiomyopathy, biopsy specimens taken from the muscular ventricular septum should be generally representative of the entire myocardium.

Including the patients in this study, myocardial biopsy has been performed on 50 patients at this hospital without mortality or significant morbidity. A major purpose of this report is to suggest that methodology allowing more precise investigation of heart muscle disease is available. Careful and selective use of these methods by qualified groups should accelerate the accumulation of knowledge of myocardial disease.

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Circulatory Responses to Beta Adrenergic Blockade with Alprenolol

Studies in Patients with Chronic Heart Disease

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Fourteen patients with acquired heart disease received 0.2 mg/kg body weight of alprenolol, a beta adrenergic blocking agent with intrinsic sympathomimetic properties, during cardiac catheterization. A high degree of beta blockade was demonstrated by injection of 3 μg of isoproterenol before and after alprenolol, the chronotropic effect of isoproterenol being almost completely abolished by alprenolol. After administration of alprenolol, significant decreases at rest and during bicycle exercise were noted in heart rate, cardiac index, maximal rate of rise of left ventricular pressure (dp/dt), left ventricular work and aortic systolic pressure, and (on exercise alone) in tension-time index and mean systolic ejection rate. Mean right atrial and pulmonary arterial pressures were significantly increased at rest after alprenolol.

In patients with heart disease, alprenolol has substantial negative chronotropic and inotropic effects, similar to those of propranolol, which are not overcome by its intrinsic beta stimulating properties.

Beta adrenergic receptor blocking agents have achieved widespread clinical use in the treatment of cardiac arrhythmias and angina pectoris.[1] Propranolol, the only beta adrenergic blocking drug currently approved for use in the United States, has negative inotropic properties that limit its effectiveness in patients with congestive heart failure or diminished myocardial reserve.[2] Alprenolol, 1-(0-allylphenoxy)-3-isopropylamino-2-propranol hydrochloride (Aptine, H56/28), a new beta adrenergic blocking agent, has recently been synthesized and introduced for study (Fig. 1). When given intravenously, it has been shown to be equipotent with propranolol in its ability to block the chronotropic and inotropic responses to isoproterenol infusion in man.[3] It is also effective in the treatment of atrial arrhythmias.[4] Moreover, in 5 normal human volunteers, alprenolol, in contrast to propranolol, caused no change in cardiac output.[5] These findings have been attributed to a mild intrinsic beta stimulating effect demonstrable in cats given reserpine and preventable by pretreatment with propranolol.[6]

The present study was undertaken to evaluate the hemodynamic effects of alprenolol in patients with chronic heart disease.

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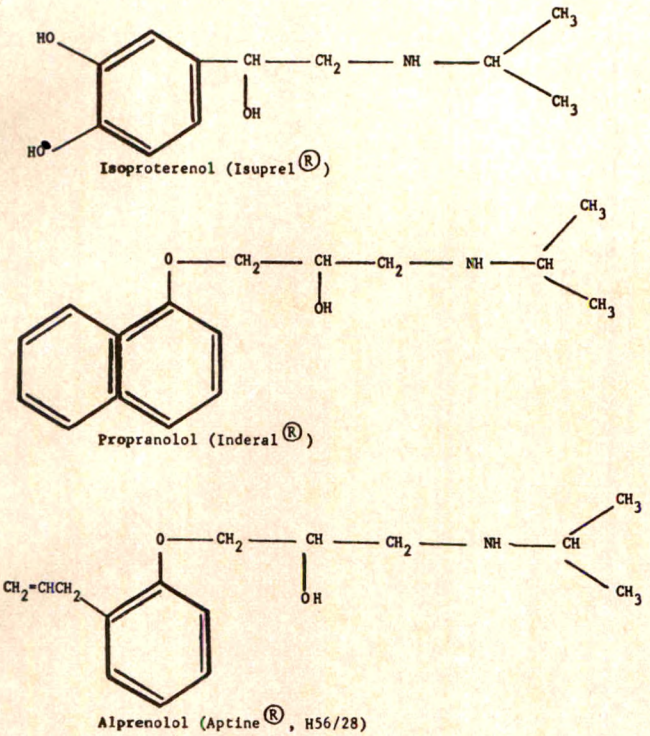

Figure 1. Chemical structures of alprenolol and (for comparison) propranolol and isoproterenol.

Material and Methods

Case material: Fourteen patients undergoing cardiac catheterization for evaluation of various forms of heart disease (Table I) were studied. Patients were asked to participate if it was considered that they could tolerate the additional time (30 minutes to 1 hour) required for the study during the course of cardiac catheterization. Patients with suspected intracardiac shunts were excluded. Informed consent was obtained from all patients.

Procedure: All patients were fasting, and received 100 mg of orally administered pentobarbital or secobarbital approximately 30 minutes before the start of the procedure. Right and left heart catheterization was performed by way of a forearm vein and the brachial or femoral artery entered percutaneously (Seldinger technique). Transseptal atrial puncture was performed in 3 patients with severe aortic stenosis in whom it was impossible to traverse the aortic valve in retrograde fashion. Pressures were recorded by use of Statham physiologic pressure mode P23db transducers. Zero pressure was taken to be at the midpoint of the thoracic anteroposterior diameter. Cardiac output was calculated by the Fick method. Oxygen consumption was determined by collecting expired air in a Collins neoprene latex meteorologic balloon and analyzing for oxygen content using a Beckman O_2 analyzer, model E2, and CO_2 content by using a Godart capnograph. Arterial and mixed venous blood oxygen content was measured by use of a Beckman spectrophotometer, model B. Maximal rate of rise of left ventricular pressure (dp/dt) was calculated by digital computer analysis of the left ventricular pressure tracing.[7]

Pressure and cardiac output measurements were made at rest and (in 9 patients) during supine exercise, using a bicycle ergometer set to a load believed to be tolerable for the patient during the 5 to 10 minute exercise period (generally 240 kg-m/min). After a rest period (at least 10 minutes), racemic alprenolol was administered intravenously in a dose of 0.2 mg/kg over 10 minutes. After an additional 20 minute interval, rest and exercise measurements were repeated. During the second exercise period, the bicycle ergometer was set to the same load as before administration of alprenolol. Each patient thus served as his own control. The maximal time elapse between the start of the drug administration and the completion of all measurements was 1 hour. No angiographic procedures were performed until all hemodynamic measurements were completed. In some patients we were not able to obtain all pressure measurements.

The following derived values were calculated:

1. Tension-time index (TTI) per beat in mm Hg seconds by using the formula: TTI = ASP × SEP, where ASP = aortic mean systolic pressure in mm Hg; SEP = systolic ejection period in sec beat.
2. Tension-time index in mm Hg seconds per min by using the formula: TTI/min = TTI/beat × HR, where HR = heart rate in beats/min.
3. Left ventricular work (LVW) in kg-m/min by using the formula: LVW = (LVSP × CO × 13.6)/1,000, where LVSP = left ventricular mean systolic pressure in mm Hg; CO = cardiac output in liters/

TABLE I

Clinical Information

Case no.	Age	Diagnosis	Functional Class*	Rhythm	Digitalis
1	66	CAD, ventricular aneurysm	IIB	NSR	—
2	50	CAD, angina	IIB	NSR	—
3	58	CAD, papillary muscle dysfunction	IIIC	NSR	+
4	32	Marfan's syndrome, AR, MR	IIB	NSR	+
5	62	RHD, MR, MS	IIIC	NSR	+
6	76	Calcific AS	IVD	AFl	+
7	57	Calcific AS	IIIC	NSR	+
8	64	CAD, RHD, MR, MS	IVD	NSR	+
9	54	RHD, AI	IIIC	NSR	+
10	62	Calcific AS	IIIC	AF	—
11	38	RHD, MS, AR	IIIC	NSR	+
12	51	Calcific AS, AR	IIIC	NSR	+
13	57	RHD, MS	IVD	AF	+
14	49	RHD, MS	IIIC	AF	+

* Classification according to criteria of the New York Heart Association.

AF = atrial fibrillation; AFl = atrial flutter; AI = aortic insufficiency; AR = aortic regurgitation; AS = aortic stenosis; CAD = coronary artery disease; MR = mitral regurgitation; MS = mitral stenosis; NSR = normal sinus rhythm; RHD = rheumatic heart disease; + = receiving digitalis; — = not receiving digitalis.

TABLE II

Hemodynamic Effects of Alprenolol at Rest and During Exercise

	Rest				Exercise			
	Control (mean ± SEM)	Alprenolol (mean ± SEM)	% Change	P Value	Control (mean ± SEM)	Alprenolol (mean ± SEM)	% Change	P Value
Heart rate (beats/min)								
All patients	85 ± 7	75 ± 6	−12	<0.01	101 ± 7	84 ± 4	−17	<0.05
Patients with NSR	76 ± 4	70 ± 4	−8	<0.05	101 ± 8	87 ± 4	−14	<0.05
Blood pressure (mm Hg)								
Aortic systolic (peak)	131 ± 5	123 ± 5	−6	<0.01	148 ± 8	132 ± 8	−11	<0.05
Aortic mean	90 ± 3	88 ± 5	−2	NS	103 ± 6	92 ± 5	−11	NS
Aortic diastolic	72 ± 5	70 ± 5	−3	NS	76 ± 5	69 ± 5	−9	NS
Right atrial mean	7 ± 1	10 ± 1	+43	<0.01	12 ± 3	14 ± 2	+17	NS
Pulmonary artery mean	30 ± 4	33 ± 4	+10	<0.01	42 ± 7	43 ± 5	+2	NS
Left ventricular end-diastolic	17 ± 3	20 ± 3	+18	NS	26 ± 5	23 ± 4	−12	NS
Cardiac index (liters/min per m^2)	2.3 ± 0.2	1.9 ± 0.1	−17	<0.01	3.3 ± 0.3	2.6 ± 0.3	−21	<0.01
Stroke index (ml/min per m^2)	29.3 ± 3.1	27.5 ± 3.0	−6	NS	33.4 ± 3.5	30.7 ± 3.5	−8	NS
Total body O_2 consumption (ml/min per m^2)	128 ± 5	122 ± 5	−5	<0.05	240 ± 20	222 ± 20	−8	<0.05
Arteriovenous O_2 difference (vol %)	5.93 ± 0.39	7.07 ± 0.60	+19	<0.01	8.45 ± 0.62	9.96 ± 0.82	+18	<0.01
Left ventricular dp/dt (mg Hg/sec)	1058 ± 72	868 ± 60	−18	<0.01	1323 ± 182	1014 ± 133	−23	<0.01
Mean systolic ejection rate (ml/sec per m^2)	108.4 ± 9.0	97.3 ± 7.9	−10	NS	112.4 ± 14.5	96.7 ± 14.8	−14	<0.05
Left ventricular work (kg-m/min)	8.58 ± 1.10	7.17 ± 0.86	−16	=0.05	12.21 ± 2.62	8.41 ± 1.88	−31	<0.01
Tension-time index per beat (mm Hg sec)	39.1 ± 3.3	40.1 ± 2.8	+3	NS	40.1 ± 4.9	35.2 ± 3.5	−13	NS
Tension-time index per minute (mm Hg sec/min)	3211 ± 425	2941 ± 342	−8	NS	3950 ± 454	2877 ± 314	−27	<0.01
LV systolic pressure × heart rate product	11982 ± 1545	9917 ± 1195	−17	NS	16291 ± 2245	11620 ± 1452	−29	<0.05
Systemic vascular resistance (units)	19.3 ± 2.2	22.7 ± 2.8	+18	NS	15.6 ± 3.0	18.0 ± 4.0	+13	NS
Pulmonary vascular resistance (units)	6.5 ± 2.7	8.2 ± 2.9	+26	NS	3.2 ± 1.2	3.9 ± 1.9	+22	NS

NS = not significant; NSR = normal sinus rhythm.

min; and 13.6 = conversion factor for the density of mercury.

4. Mean systolic ejection rate (SER) in ml/sec per m^2 by using the formula, SER = SI/SEP, where SI = stroke index in ml/m^2; and SEP = systolic ejection period in sec/beat.

5. Pulmonary vascular resistance (PVR) in arbitrary resistance units (ru) by using the formula: PVR = (PAm − PAWm)/CO, where PAm = mean pulmonary arterial pressure in mm Hg; PAWm = mean pulmonary arterial wedge pressure in mm Hg; CO = cardiac output in liters/min.

6. Systemic vascular resistance (SVR) in arbitrary resistance units (ru) by using the formula: SVR = (Aom − RAm)/CO, where Aom = mean aortic pressure in mm Hg; and RAm = right atrial mean pressure in mm Hg.

7. The product of left ventricular peak systolic pressure and heart rate in arbitrary units.

These values were not derived in all patients if the tracings were believed not adequate to permit accurate calculation. Data were analyzed for statistical significance by use of a paired *t*-test.

Results

Twelve patients were given isoproterenol hydrochloride, 3 μg, as a rapid intravenous "bolus" injection, and the effect on heart rate was measured. This was done after taking the initial resting pressure measurements, and was repeated after the taking of the postalprenolol resting measurements, generally 30 to 40 minutes after the start of alprenolol administration. The average maximal heart rate increase after the first challenge of isoproterenol was 23 ± 5 beats/min, whereas after administration of alprenolol an average maximal increase of only 1 ± 1 beat/min occurred with isoproterenol ($P < 0.01$).

The hemodynamic results of administration of alprenolol are summarized in Table II. Significant

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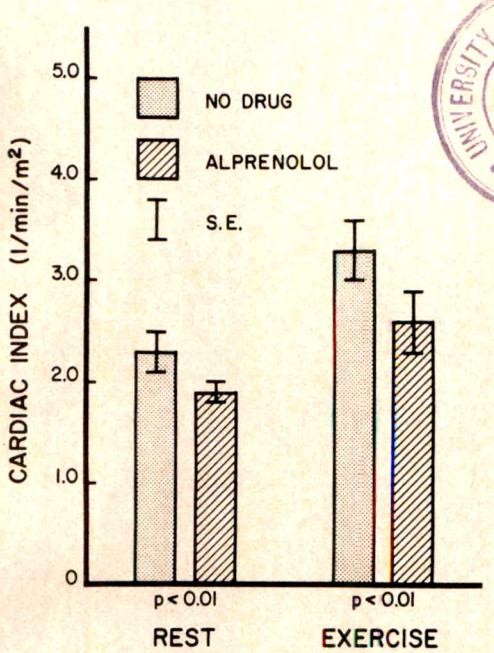

Figure 2. Response of cardiac index to alprenolol infusion at rest and exercise.

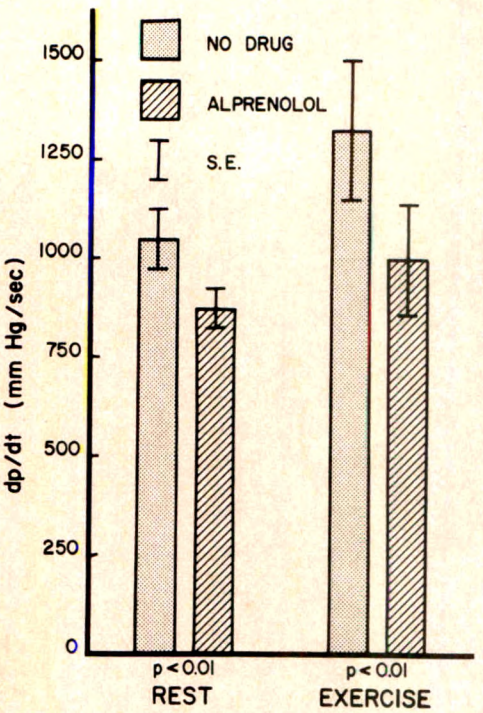

Figure 3. Response of maximal rise of left ventricular peak dp/dt to alprenolol infusion at rest and exercise.

decreases after alprenolol administration were noted in values for heart rate, aortic systolic pressure, cardiac index (Fig. 2), left ventricular dp/dt (Fig. 3) and left ventricular work. Decreased values for mean systolic ejection rate, tension-time index per minute (Fig. 4) and the product of left ventricular systolic pressure and heart rate were statistically significant on exercise but not at rest, whereas changes in tension-time index per beat were not significant in either condition. Mean right atrial and pulmonary arterial pressures rose significantly at rest, but not on exercise. Changes in aortic mean and diastolic pressure, left ventricular end-diastolic pressure, stroke index and systemic and pulmonary vascular resistance were not significant.

Discussion

The negative chronotropic effects of alprenolol, shown previously in supraventricular arrhythmias,[4] were again demonstrated in this group of 14 patients, 10 of whom had sinus rhythm. Using somewhat smaller doses of alprenolol, other investigators have demonstrated decreases in heart rate of 12[8] and 13 percent[9] at rest in patients with acute myocardial infarction and other forms of heart disease. We found a drop of 8 percent at rest and 14 percent on exercise. The greater effect of alprenolol during exercise seen in this and several other hemodynamic indexes is presumably related to the significant role played by sympathetic stimulation of the heart in the circulatory response to exercise.[10]

Myocardial contractility: Cardiac index fell significantly at rest and exercise after administration of alprenolol, as did maximal left ventricular dp/dt and mean systolic ejection rate (the latter changed significantly only on exercise). These changes are in large part related to the slowing of heart rate induced by alprenolol, as indicated by the not statistically significant change in the stroke index. In 4 patients at rest and in 2 on exercise, there was no slowing of heart rate after administration of alprenolol: in 1 patient (Case 12), the

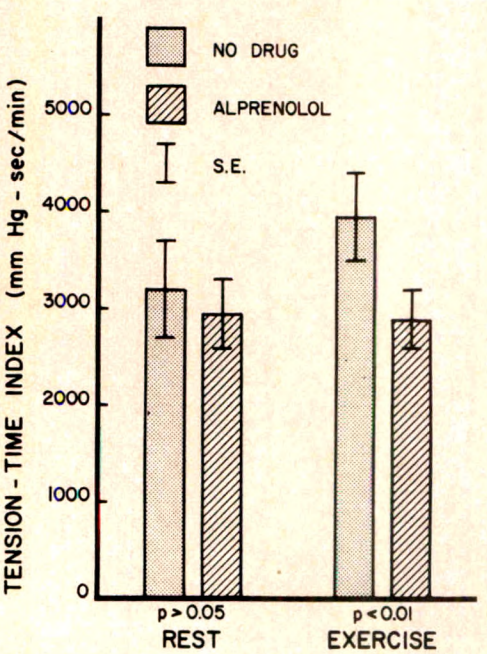

Figure 4. Response of tension-time index per minute to alprenolol infusion at rest and exercise.

TABLE III

Hemodynamic Effects of Alprenolol in Patients Not Demonstrating a Decline in Heart Rate After Drug Administration

Case no.	Condition	Heart Rate (beats/min)	Cardiac Index (liters/min per m²)	Stroke Index (ml/min per m²)	A–V O_2 Diff. (vol. %)	LVSPm (mm Hg)	LVEDP (mm Hg)	dp/dt (mm Hg/sec)	MSER (ml/sec per m²)	LVW (kg-m/min)	TTI/beat (mm Hg/sec)	TTI/min (mm Hg/sec per min)	$LVSP_p$ × Heart Rate
6	R, C	140*	1.4	10	9.4								
	D	140*	1.1	8	11.4								
7	R, C	54	2.5	46	5.2	152	10	1,268	135.3	113.72	51.7	2,791	11,664
	D	54	2.3	43	5.5	144	12	1,060	122.9	99.94	50.4	2,721	10,044
7	E, C	74	3.6	49	7.2	200	29	1,629	144.1	212.20	68.0	5,032	16,800
	D	74	2.8	38	8.6	150	32	1,180	115.6	126.57	48.0	3,660	15,300
9	R, C	72	2.3	32	7.0		39						9,504
	D	72	1.3	18	10.2		37						9,072
12	R, C	80	2.5	31	6.7	158	40	1,275	106.9	105.31	45.8	3,660	14,960
	D	90	2.1	23	7.2	158	42	1,073	79.3	92.44	45.8	4,120	15,840
14	E, D	75	2.8	37	7.9	100	6		123.3	63.9	30.0	2,250	9,375
	D	75	2.6	35	9.5	110	10		106.0	65.8	36.3	2,723	10,500

* = atrial flutter.

A–V O_2 Diff. = arteriovenous oxygen difference; C = control; D = drug administration; dp/dt = maximal rate of rise of left ventricular pressure; E = exercise; LVEDP = left ventricular end-diastolic pressure; LVSPm = left ventricular mean systolic pressure; LVSPp = left ventricular peak systolic pressure; LVW = left ventricular minute work; MSER = mean systolic ejection rate; R = rest; TTI = tension-time index.

TABLE IV

Hemodynamic Effects of Propranolol and Alprenolol in Patients with Heart Disease at Rest and During Exercise*

Author	Propranolol Dose (mg/kg)	Heart Rate (%)	Cardiac Index (%)	Stroke Index (%)	Ao Mean Pressure (%)	RA Mean Pressure (%)	PA Mean Pressure (%)	LVEDP (%)	SVR (%)	MSER (%)	dp/dt (%)	LVW (%)	TTI per min (%)
Rest													
Sonnenblick et al.[20]	0.17	−12	−19†	−2‡						−2	−2		
Sowton and Hamer[27]	5 mg	−10	−20†	−15	−4		−7					−21	
Wolfson et al.[14]	5 mg	−12	−13†	0‡				−30					
Robin et al.[28]	0.10	−14	−38	−27	−1			+197	+70	−32	−26	−40	−6
Parker et al.[29]	0.15	−15	−15	−6		+8	−8					−20	−5
Ulrych et al.[24]	10 mg	−13	−20	−7	0				+20	−15			
Lund-Larsen & Sivertssen[8]	5 mg	−12	−25	−12	−4	+50			+25				
Alprenolol study	0.20	−8	−17	−6	−2	+43	+10	+18	+18	−10	−18	−16	−3
Exercise													
Epstein et al.[10]	0.15	−19	−22†		−15				0			−34	
Sonnenblick et al.[20]	0.17	−26	−25†	−10‡						−16	−22		
Sowton and Hamer[27]	5 mg	−15	−20†	−5‡	3		+10					−24	−8
Parker et al.[29]	0.15	−15	−20	−1	−7		+20	+5		−8		−27	−20
Alprenolol study	0.20	−14	−21	−8	−11	+17	+2	−12	+13	−14	−23	−31	−27

* Data expressed as percentage changes before and after propranolol administration. Not all changes are statistically significant; † = cardiac output; ‡ = stroke volume.

Ao = aortic; RA = right atrial; SVR = systemic vascular resistance; other abbreviations as in Table III.

heart rate before administration of alprenolol was 80/min and after administration 90/min, possibly due to incomplete recovery from an intervening exercise period. In these 6 cases, the hemodynamic data (Table III) still reveal significant decreases in cardiac and stroke index, dp/dt and mean systolic ejection rate—changes that cannot be attributed to alteration in heart rate. Since peak dp/dt and mean systolic ejection rate have been noted to bear a relation to myocardial contractility,[11,12] alprenolol would appear to have negative inotropic effects independent of its negative chronotropic effects. Alterations in left ventricular systolic and end-diastolic pressures and the product of systolic pressure and heart rate, which have also been shown to affect peak dp/dt,[11] were not of sufficient magnitude to account for the changes in dp/dt observed in this group of patients.

Myocardial oxygen requirements: Beta adrenergic receptor blocking agents have proved effective in the treatment of angina pectoris,[13] probably by lessening myocardial oxygen requirements,[14] especially in response to exercise.[15] Myocardial oxygen demand has been shown to be correlated with a number of factors, including the area beneath the systolic pressure curve (tension-time index),[16] peak systolic ventricular pressure,[17] the product of peak ventricular pressure and heart rate,[18,19] and left ventricular external work.[20] All of these measures except the tension-time index showed significant declines at rest and exercise after alprenolol. The tension-time index per beat did not vary significantly after alprenolol, but the tension-time index per minute showed an 8 percent fall at rest (not significant) and a 27 percent fall on exercise ($P < 0.01$). Alprenolol thus lowers myocardial oxygen demand, which may account for its reported successes in the treatment of angina.[21,22] Of note is the lack of consistent decreases in these indexes in patients whose heart rate did not decline after administration of alprenolol (Table III); in some patients (Cases 12 and 14) the indirectly estimated myocardial oxygen demand appeared to increase. This suggests that the antianginal effects of alprenolol may be dependent on heart rate.

Arterial pressure: Aortic systolic pressure fell after administration of alprenolol, 6 percent at rest ($P < 0.01$) and 11 percent on exercise ($P < 0.05$). Decreases in aortic diastolic and mean pressure (9 and 11 percent, respectively) occurred on exercise but were not statistically significant. Prolonged treatment of hypertensive patients with orally administered propranolol also results in a fall in the level of arterial pressure attributed to decreased cardiac output.[23] Of note is the observation that acute intravenous infusion of propranolol fails to reduce arterial pressure immediately,[24] in contradistinction to our systolic pressure findings with alprenolol.

Clinical implications: Our findings are in striking contrast to the results of Forsberg and Johnson,[5] who administered 10 mg of alprenolol to 5 normal human volunteers and reported no statistically significant variation in heart rate, arterial pressure, cardiac output, stroke volume and right atrial pressure. They attributed these findings to alprenolol's mild intrinsic beta receptor stimulating action[6] and postulated that the latter caused cardiac stimulation sufficient to overcome the depressant effect of the beta receptor blockade. Patients with congestive heart failure are dependent on an increased sympathetic tone to maintain cardiac output.[25] In such persons, beta adrenergic receptor blockade would be expected to have more profound effects than in the normal subject in the supine, resting position, with a low level of sympathetic activity. Since most of our patients had severe, symptomatic heart disease with congestive heart failure and were generally in functional class 3 or 4 (New York Heart Association), as suggested by the low resting control mean cardiac index of 2.3 ± 0.2 liters/min per m^2, they would be expected to be more dependent on increased sympathetic tone to maintain cardiac output. In this clinical setting the mild sympathomimetic effects of alprenolol would appear inadequate to compensate for the hemodynamic consequences of beta adrenergic blockade.

The dose of alprenolol (0.2 mg/kg) employed in this study is somewhat higher than that used by previous investigators. It was chosen because previous work suggested this dose to be effective in the treatment of supraventricular arrhythmias.[4] Ventricular ectopic beats and ventricular tachycardia have also been treated with intravenously administered alprenolol in dosages similar to ours.[26] We did not investigate the hemodynamic effects of orally administered alprenolol, as would be utilized in the long-term treatment of chronic arrhythmias or angina.

Comparison of alprenolol and propranolol: The hemodynamic effects of propranolol in heart disease have been extensively studied.[8,10,14,27–29] These studies are summarized in Table IV, and the data from this study of alprenolol have been included for comparison. It can be seen that in all hemodynamic indexes measured, the 2 agents are essentially similar. Thus, in the dosage employed in this study, the cardiovascular effects of alprenolol are comparable to those of propranolol in patients with heart disease.

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Dietary Salt and Essential Hypertension

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Dietary intake of sodium chloride was studied in 717 patients with essential hypertension and 819 unequivocally normotensive patients. In the normotensive group 21.2 percent (174 of 819) stated that they added salt to food before tasting it, whereas 22.7 percent (163 of 717) of the hypertensive group had this habit. Of 43 hypertensive women who added salt to food before tasting it, 17 (39.5 percent) had diastolic blood pressure greater than 120 mm Hg, compared to 56 (17.2 percent) of 325 hypertensive women who did not add salt before tasting the food ($P < 0.0006$). Of 43 hypertensive women who added salt before tasting, 5 (11.6 percent) had either or both retinal hemorrhages and exudates with or without papilledema; of 314 women who did not add salt before tasting, only 8 (2.6 percent) had retinopathy of this severity ($P < 0.003$). Salt consumption did not influence the severity of hypertension in men as reflected by diastolic blood pressure or hypertensive retinopathy. However, hypertensive heart disease manifested by electrocardiographic evidence of left ventricular hypertrophy or roentgenographic evidence of cardiomegaly, or both, was encountered in 47 (39.2 percent) of 120 hypertensive men who salted their food before tasting it, compared to 51 (22.3 percent) of 229 hypertensive men who did not add salt before tasting ($P < 0.0008$). Salt consumption made no difference with regard to the prevalence of hypertensive heart disease among women.

Hypertension was more prevalent among patients with a family history of hypertension than among those without such a history. No significant differences were found between hypertensive and normotensive patients in regard to dietary history of salt consumption. However, dietary salt consumption may play a role in determining the severity of hypertension once it has developed.

The relation between the sodium ion and the development of hypertension remains obscure. An early scientific observation that dietary restriction of sodium chloride might ameliorate human hypertension was published by Ambard and Beaujard[1] in 1904. In 1940 Grollman et al.[2] demonstrated in animal experiments that adrenocortical steroids produced hypertension only when additional salt was provided. Kempner[3,4] favorably influenced hypertensive disease through the use of a rice and fruit diet; it was later shown[5] that the effect of the diet was due primarily to its low sodium content.

It is generally believed that the level of blood pressure is determined by many factors, both constitutional and environmental. Dahl and co-workers[6–11] have proposed and demonstrated by investigations in animals and man that excessive ingestion of salt may be a factor in the development of hypertension. From popula-

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TABLE I

Relation Between Subjective Estimate of Salt Consumption and Urinary Sodium Excretion in 47 Patients with Essential Hypertension

Patient's Description of Salt Consumption	no. of Patients	Average Urinary Sodium (mEq/24 hours)	Standard Deviation
Group A (salt not added before tasting)	31	111*	51
Salt never added	12	111	62
Salt added occasionally	8	93.5	47
Salt added to taste	11	124	40
Group B (salt added before tasting)	16	151*	58

* P = <0.05.

tion studies in various geographic areas Dahl[12] demonstrated a significantly lower prevalence of hypertension in societies and racial groups with a low content of sodium in their diets than in groups with a high dietary content of sodium.

The purpose of this study was to determine in a large group of patients the relation of dietary intake of sodium chloride to the prevalence and severity of hypertension, with consideration of the additional influence of genetic predisposition to hypertension (as demonstrated by a positive family history of hypertension).

Materials and Methods

Each of 1,536 out-patients who consulted one of us (R. W. G.) for complete diagnostic evaluation during a 4 year period from 1961 to 1965 was questioned by this investigator in regard to dietary sodium habits, and then was assigned to 1 of the following 4 categories: category 1, patients who never added salt to their food under any circumstances; category 2, patients who did not usually add salt to their food; category 3, patients who added salt to their food to suit their tastes; and category 4, patients who habitually added salt to their food before tasting it.

Dietary salt habits appeared to be life-long insofar as patients could remember. On the advice of their physicians, a few patients had been on low sodium diets for several weeks to several years at the time of initial interview. For purposes of classifying these patients, only the dietary salt habits before enforced limitation were considered.

The quantity of sodium in a 24 hour urine specimen was measured for each of 47 of the patients under conditions of their usual diets and at a time when they were taking no medications. Patients who were limiting the salt in their diet on advice of their physicians were not selected for this part of the study. Of these patients, 32 had essential hypertension. The purpose of this portion of the study was to determine whether the amount of sodium excreted correlated with the patient's estimate of the amount of sodium ingested.

The following information was also obtained from the patients' records: age, sex, initial blood pressure (supine, sitting and standing), height, weight, duration of hypertension when present, antipressor therapy, if any, family history of hypertension or vascular disease, and ophthalmoscopic grouping of hypertension according to the Keith-Wagener-Barker classification. Patients with secondary hypertension were excluded from the study. Hypertension was defined as initial systolic blood pressure greater than 140 mm Hg or initial diastolic pressure greater than 90 mm Hg, or both.

Correlative analyses were made of the severity of hypertension (as estimated from ophthalmoscopic changes, diastolic blood pressure, electrocardiographic changes, and cardiac size and configuration on roentgenogram) with dietary salt habits. The prevalence of a positive family history of hypertension was estimated for each dietary group.

Results

Of the 1,536 patients of this study, 717 had essential hypertension, and 819 were unequivocally normotensive.

Urinary sodium excretion: Of the 47 subjects whose urinary sodium excretion level was studied, 16 patients (group B) added salt to their food before tasting. Their average sodium excretion level was 151 mEq/24 hours (Table I). Of 31 subjects who did not add salt before tasting (group A) there were 3 subgroups: (1) 12 patients who never added salt to their food (average sodium excretion 111 mEq/24 hours); (2) 8 patients who added salt occasionally (average sodium excretion 93.5 mEq/liter); and (3) 11 patients who added salt to taste (average sodium excretion 124 mEq/liter) (Table I). For all 31 patients in group A, the average 24 hour sodium excretion level was 111 mEq/liter. The difference between the averages of groups A

TABLE II

Dietary Salt Habits of Normotensive and Hypertensive Patients

Dietary Salt Group	Normotensive				Hypertensive			
	no. of Men	no. of Women	Total	%	no. of Men	no. of Women	Total	%
Group A (salt not added before tasting)	297	348	645	78.8	229	325	554	77.3
Group B (salt added before tasting)	135	39	174	21.2	120	43	163	22.7
Total	432	387	819	100.0	349	368	717	100.0

and B (111 versus 151) was statistically significant ($P < 0.05$). There was no significant difference among the subgroups of group A or between group B and any subgroup of group A. As a result, statistical analyses were confined to the 2 main groupings, that is, group A (patients who did not add salt before tasting) and group B (patients who added salt before tasting).

Dietary salt habits of normotensive patients (Table II): There were 819 normotensive patients of whom 432 (52.7 percent) were men and 387 (47.3 percent) women. Of 432 normotensive men 69 percent, and of 387 normotensive women 90 percent were in group A. Of the total group, 174 (21.2 percent) were in group B (salt added before tasting), while 645 (78.8 percent) gave a history of lesser salt consumption and were therefore placed in group A. The proportion of male subjects was 46 percent (297 of 645) in group A and 77.6 percent (135 of 174) in group B.

Dietary salt habits of patients with essential hypertension (Table II): Of the 717 patients with essential hypertension, 349 (48.7 percent) were men and 368 (51.3 percent) were women. Of these hypertensive patients, 66 percent of the men and 88 percent of the women were in group A. Of the total, 554 (77.3 percent) were in group A, whereas 163 (22.7 percent) were in group B. The proportion of men was 41.3 percent (229 of 554) in group A and 73.6 percent (120 of 163) in group B.

There was no statistically significant difference between the hypertensive and normotensive patients with regard to dietary salt habits. There was a significantly greater percentage of men in group B than in group A ($P < 0.0001$) in both the normotensive (77.6 versus 46.0 percent) and hypertensive (73.6 versus 41.3 percent) categories.

TABLE III

Relation Between Dietary Salt Habits and Ophthalmoscopic Classification in Patients with Essential Hypertension

Dietary Salt Group	no. of Patients	Patients with Severe Retinopathy*	
		no.	%
Group A	534†		
Women	314	8	2.6‡
Men	220	6	2.7
Group B	158§		
Women	43	5	11.6‡
Men	115	7	6.1

* Keith-Wagener-Barker groups 2+, 3 or 4 (hemorrhages or exudates, or both, with or without papilledema).

† Excludes 20 patients who did not have ophthalmoscopic examinations.

‡ Difference is statistically significant ($P < 0.003$).

§ Excludes 5 patients who did not have ophthalmoscopic examinations.

TABLE IV

Relation Between Dietary Salt Habits and Diastolic Blood Pressure in Patients with Essential Hypertension

Dietary Salt Group	no. of Patients	Patients with Diastolic Blood Pressure > 120 mm Hg	
		no.	%
Group A	554		
Women	325	56	17.2*
Men	229	52	22.7
Group B	163		
Women	43	17	39.5*
Men	120	32	26.6

* Difference is statistically significant ($P < 0.0006$).

Severity of hypertension and dietary salt habits: The severity of hypertension in the 717 patients with essential hypertension, as estimated from retinal changes and level of diastolic blood pressure, was correlated with the dietary salt habits of these patients.

Ophthalmoscopic findings (Table III). Ophthalmoscopic examinations were reported for all but 25 patients with essential hypertension. The proportion of patients with retinal hemorrhages or exudates, or both, with or without papilledema (Keith-Wagener-Barker groups 2+, 3 and 4) was compared in the 2 categories of dietary salt intake. There was a statistically significantly greater percentage of women with severe retinopathy in group B than in group A ($P < 0.003$). There was no significant difference between the percentages of men with severe retinopathy in these 2 categories of salt consumption.

Diastolic blood pressure and dietary salt habits (Table IV). The 39.5 percent of 43 women in group B with at least 1 diastolic blood pressure measure-

TABLE V

Relation Between Dietary Salt Habits and Either or Both the Presence of Cardiomegaly and Electrocardiographic Changes of Left Ventricular Hypertrophy in Patients with Essential Hypertension

Dietary Salt Group	no. of Patients	Patients with Cardiomegaly and/or ECG Changes of LVH	
		no.	%
Group A	554		
Women	325	71	21.8
Men	229	51	22.3*
Group B	163		
Women	43	11	25.6
Men	120	47	39.2*

* Difference is statistically significant ($P < 0.0008$).

ECG = electrocardiographic; LVH = left ventricular hypertrophy.

TABLE VI

Relation Between Dietary Salt Habits and Family History of Hypertension in Patients with Essential Hypertension

Dietary Salt Group	no. of Patients*	Patients with Family History of Hypertension	
		no.	%
Group A	381	231	60.6
Women	219	139	63.5†
Men	162	92	56.8
Group B	117	70	59.8
Women	32	26	81.3†
Men	85	44	51.8

* Patients for whom adequate information on family history was recorded.

† Difference is statistically significant ($P < 0.05$).

ment higher than 120 mm Hg was significantly greater ($P < 0.0006$) than the 17.2 percent of 325 women in group A with this degree of elevation of diastolic blood pressure level. There was no significant difference between the percentages of men with diastolic blood pressures greater than 120 mm Hg in groups A and B.

Hypertensive heart disease (Table V). Men in group B had a significantly ($P < 0.0008$) greater prevalence (39.2 percent of 120 patients) of hypertensive heart disease (cardiomegaly or electrocardiographic changes suggestive of left ventricular hypertrophy, or both) than did the men in group A (22.3 percent of 229). There was no significant difference in the prevalence of hypertensive heart disease between women in groups A and B.

Association of family history and dietary salt habits in patients with essential hypertension: Information relative to family history was available for 498 patients with essential hypertension (Table VI). In group A, 231 of 381 patients (60.6 percent) had a family history of hypertension in at least 1 parent, sibling or grandparent. In group B, 70 of 117 patients (59.8 percent) had a family history of hypertension. There was a significantly ($P < 0.05$) greater percentage of women with a family history of hypertension in group B than in group A (81.3 percent versus 63.5 percent). There was no significant difference in this index between men in groups A and B.

In the entire group, including both normotensive and hypertensive persons (Table VII), there was a significantly ($P < 0.0005$ to $P < 0.005$) greater percentage of hypertensive persons in the group who had a family history of hypertension. Salt intake did not appear to affect this prevalence of hypertension since there was no significant difference between subjects in groups A and B in this regard.

There was no significant difference in the prevalence of a family history of vascular disease (myocardial infarction or cerebral vascular accident, or both) or diabetes mellitus between patients in group A and group B.

TABLE VII

Relation of Family History of Hypertension and Dietary Salt Habits to the Prevalence of Hypertension

Family History of Hypertension	Sex	Group A		Group B	
		no. of Patients	Hypertensive (%)	no. of Patients	Hypertensive (%)
Negative	M	153	46*	94	44†
	F	175	46‡	23	26§
Positive	M	148	62*	65	68†
	F	230	60‡	36	72§
Not stated or uncertain	M	225	30	96	36
	F	268	40	23	48
Total		1199			

* Difference is statistically significant ($P < 0.005$); † difference is statistically significant ($P < 0.003$); ‡ difference is statistically significant ($P < 0.005$); § difference is statistically significant ($P < 0.0005$).

Discussion

Dahl and Love[7] stated that the following 3 observations implicated sodium in the origin of essential hypertension: (1) the need for sodium in the production of certain forms of experimental hypertension; (2) the virtual absence of hypertension among primitive races, all of whom appear to have a low sodium diet; and (3) the amelioration of hypertension in some persons by dietary restriction of sodium. Dahl and Love[7] classified according to their habitual consumption of table salt more than 1,300 adults who reported for annual physical examinations, and correlated their observations with blood pressure determinations. They concluded that the "group with low salt intake had significantly less and the group with high salt intake significantly more hypertension than would be expected from random distribution." This finding suggested to them that the consumption of salt was an important etiologic factor in the development of essential hypertension.

Dahl[12] later reported that a direct correlation existed between average salt consumption and the prevalence of hypertension in different geographic areas and in different racial groups. Prior et al.[13] showed that between 2 Polynesian population groups the 1 with the higher average of salt consumption had a higher prevalence of hypertension.

These observations in man have counterparts in animal experiments. Meneely and colleagues[14] showed that when the salt consumption of rats was increased, the incidence and severity of elevated blood pressure also increased.

Salt ingestion and prevalence of hypertension: The present findings do not confirm the previous

observations in regard to the relation between salt ingestion and the prevalence of hypertension in man. There was no significant difference between the normotensive and hypertensive patients with regard to dietary salt habits. These findings are in agreement with the reports of Schneckloth et al.,[15] who showed that there were no differences in salt consumption among subjects with different levels of blood pressure, and of Whyte,[16] who noted similar blood pressure values in groups assumed to have differences in salt intake.

It has previously been suggested[17] that persons with hypertension have an increased appetite for salt. The fact that the hypertensive patients and the normotensive patients in our study had almost identical habits with regard to salt consumption would tend to disprove this theory. It is not known why men, whether hypertensive or normotensive, tended to consume larger amounts of salt than women.

Salt ingestion and severity of hypertension: Although this study indicates that there seems to be no relation between the prevalence of hypertension and dietary salt habits, excessive consumption of salt seemed to make hypertension more severe once it was present. Diastolic blood pressure greater than 120 mm Hg, severe hypertensive retinopathy (Keith-Wagener-Barker classifications 2+, 3 or 4), roentgenographic evidence of cardiac enlargement and electrocardiographic changes of left ventricular hypertrophy were all used as indexes of "severe hypertension." There was a significantly greater percentage of patients with severe hypertension as defined by any of these criteria in group B than in group A, thus suggesting that excessive salt ingestion seemed to influence adversely the severity of hypertension once it had developed. Among hypertensive women, excessive salt ingestion was associated with increased prevalence of diastolic blood pressure greater than 120 mm Hg and severe hypertensive retinopathy, whereas among men there was a significant relation between excessive salt ingestion and the prevalence of hypertensive heart disease as manifested by electrocardiographic findings of left ventricular hypertrophy or evidence of cardiac enlargement on chest roentgenograms, or both. No explanation is apparent for this difference between the sexes in the way excessive ingestion of sodium tended to aggravate hypertensive cardiovascular disease.

Because we were primarily interested in relating salt ingestion to prevalence of hypertension, we elected to classify patients according to their life-long dietary salt habits, even though a few were limiting salt in their diets on the advice of their family physicians when they were first examined. For those patients, severity of hypertension at the time they were examined at the Clinic was also related to previous dietary salt habits, even though the low sodium diets they had been advised to consume more recently might have modified the severity of the hypertension. It is unlikely that this would materially affect the results for the following reasons: (1) only a few patients were attempting to limit salt in their diet and these were proportionately distributed between groups A and B; (2) experience has shown that many patients do not adhere closely to a low sodium diet even though advised to do so; (3) it seems reasonable to assume that dietary sodium restriction would have a greater hypotensive effect in group B than in group A so that, if anything, the differences in severity of hypertension observed between these 2 groups would be greater, not less, if some of the patients in each group had not been on low sodium diets.

Although many of the patients in both groups were receiving antihypertensive medication (usually including a diuretic agent) at the time they were evaluated at the Cleveland Clinic, it is doubtful that therapy can explain all of the highly significant differences in severity of hypertension between these 2 groups. Again, it is plausible to assume that diuretic therapy would have a greater hypotensive effect in the patients on a high sodium diet (group B) than in patients consuming lesser quantities of sodium (group A). If this is so, therapy would tend to lessen, not increase the difference in severity of hypertension between groups A and B.

Hereditary and familial factors: It has been suggested that a genetic factor is operative in the development of hypertension and that the addition of environmental factors such as excessive salt consumption is responsible for unmasking this trait.[9] These conclusions have been supported by animal experiments with the selective inbreeding of Sprague-Dawley rats. Two strains evolved; in 1, hypertension developed upon the addition of a high salt diet, whereas the other strain remained normotensive on the same diet. It is generally accepted that hereditary factors are operative in the development of human hypertension. Thomas[18] studied the prevalence of hypertension in 2 successive generations of subjects and found that the greatest proportion of persons with hypertension always occurred among subjects who had 2 hypertensive parents. Our study showed a greater prevalence of hypertension among patients with a family history of hypertension. There was no significant difference in the prevalence of hypertension between the 2 groups of salt users.

The results of the present investigation indicate that family history of hypertension has a greater influence on the development of hypertension in an individual than a history of excessive salt consumption. However, excessive salt consumption appears to affect adversely the severity of existing hypertension.

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Myocardial Anaerobiosis in Anemia in Uremic Man

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Myocardial anaerobic metabolism (lactate production) has been previously observed in man primarily in ischemic heart disease. Myocardial lactate balance was studied in severe anemia in 6 stable uremic patients receiving maintenance hemodialysis before and after transfusion. They were young, aged 21 to 31, and had no evidence of heart disease or angina pectoris.

At rest, the mean extraction coefficient for lactate by the myocardium $(A–V/A)_L$ was abnormally low at —1.2 percent (range 14.3 to —18.9 percent). Intravenous isoproterenol infusion (2 to 8 μg/min) resulted in definite anaerobiosis in all patients, mean $(A–V/A)_L$ —29.9 percent (range —1.5 to —76.5 percent). After transfusion, the extraction coefficient at rest was normal, mean 22 percent (range 11 to 39 percent), and decreased with isoproterenol infusion but remained positive in 5 of 6 patients.

Electrical pacing (mean heart rate 148 beats/min) before transfusion increased the average extraction coefficient from 5.9 percent at rest to 7.9 percent; after transfusion, extraction increased from 22.9 percent to 34.3 percent. Exercise changes were not significant. Lactate/pyruvate ratio tended to increase from artery to coronary sinus during stress, before transfusion. There was improvement in the extraction coefficient for lactate with transfusion, without alteration of the uremic state. Cardiac index and systolic ejection rates indicated a hyperkinetic circulation at rest, increased by isoproterenol and exercise, and decreased by transfusion.

Compensatory myocardial anaerobiosis may thus occur in physiologically stable anemic uremic patients with normal hearts and without development of angina.

Myocardial metabolism in man is normally aerobic, and lactate is consumed as a substrate for energy production by the heart in proportion to its concentration in arterial blood.[1] Increases in demand for energy are met by an increase in coronary blood flow within wide limits, rather than by increased oxygen extraction. Anaerobic metabolism in the heart has been associated primarily with myocardial ischemia secondary to coronary insufficiency,[2–6] and probably with marked left ventricular hypertrophy associated with aortic stenosis. Lactate production by the normal heart associated with anemia has not been observed previously in man. In this study myocardial anaerobiosis in 6 anemic uremic patients with a normal heart was shown during 1 or more stressful situations. The negative arterial-coronary sinus (A–CS) difference for lactate reverted to positive after transfusion. The production of lactate by the heart is associated with the development of anaerobic heat; therefore, a reversal of myocardial arteriovenous differ-

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TABLE I

Clinical and Laboratory Data of Study Patients

Case no.	Age (yr) & Sex	Diagnosis	Hematocrit (%) Before Transfusion	Hematocrit (%) After Transfusion	Usual Blood Pressure (mm Hg)	ECG QRS Voltage ($SV_1 + RV_5$) (mm)	Cardiothoracic Ratio on Chest Roentgenogram (cm)	Usual Blood Urea Nitrogen (mg/100 ml) Before Dialysis	Usual Blood Urea Nitrogen (mg/100 ml) After Dialysis
1	29M	Chronic glomerulonephritis	16	24	140/90	35	12/25	85	26
2	26M	Chronic glomerulonephritis	20	26	130/70	35	13/28	80	25
3	21F	Nephrophthisis	17	23	90/60	30	10/24	50	15
4	31M	Hereditary interstitial nephritis	21	28	160/110	25	12/27	75	22
5	22M	Chronic glomerulonephritis	15	25	140/80	45	12/26	65	18
6	21M	Chronic glomerulonephritis	14	21	150/110	25	13/27	110	35

ence for lactate in the steady state may be equated with anaerobic metabolism.[7] Thus, it is inferred that during moderately severe anemia, a normal coronary circulation is inadequate to meet a demand for oxygen and energy substrates by flow alone, and the heart resorts to anaerobic energy production.

Methods

The patients were 5 men and 1 woman ranging in age from 21 to 31 years. Clinical data are given in Table I. All patients had chronic renal insufficiency of varying origin, and were being maintained in good medical condition on chronic hemodialysis (5 patients) or intermittent peritoneal dialysis (1 patient). Four of the patients were sufficiently well to continue their usual occupations. Only 1 (Case 6) was hospitalized at the time of the study; the others were admitted only for the purpose of the procedure. The studies were performed in the period after dialysis. Fully informed consent was obtained from each patient. No patient had ever had chest discomfort or clinical evidence suggestive of myocardial infarction or heart disease. Only 1 patient (Case 4) had persistent hypertension. In Case 6 the hypertension was probably related to fluid overload (Table I). No patient had evidence of pulmonary congestion. Electrocardiograms showed no evidence of left ventricular hypertrophy or electrolyte imbalance, and chest roentgenograms revealed normal cardiac size. All patients were chronically anemic with hematocrit values immediately before the study of 14 to 21 percent.

Coronary sinus catheterization was performed using intramuscular meperidine, 50 mg, and promethazine hydrochloride, 25 mg, as premedication, and 2 percent lidocaine for local anesthesia. The patients fasted overnight. A polyethylene catheter (PE 150) was inserted percutaneously into the brachial artery by the Seldinger technique. A no. 7 Goodale-Lubin catheter was introduced into the coronary sinus under fluoroscopic control. A no. 6 bipolar pacing catheter was introduced into the right atrium by means of a venotomy, sometimes in the same vein as that used for the coronary sinus catheter. Arterial pressures were measured with a Statham P23Db strain gauge transducer and recorded with an Electronics for Medicine DR8 recorder. Cardiac output was determined in duplicate by the indicator-dilution method on a Gilford 103IR and 104 densitometer and computer. Indocyanine green dye was injected into the coronary sinus and sampled through a sterile system from the brachial artery. Blood was returned to the patient after each determination. Reproducibility of the method in our laboratory is 5 percent from the mean.

Lactate and pyruvate measurements were performed in duplicate on the arterial and coronary sinus blood samples drawn simultaneously into dry syringes over 10 to 15 seconds and injected immediately into ice-cold 10 percent perchloric acid. The lactate and pyruvate determinations were performed by modifications of enzymatic methods of Horn and Bruns[8] and Redetzki et al.,[9] respectively. Standards were measured with each set of unknowns; recovery was above 95 percent.

The protocol included 3 methods of stress, performed in the following order: (1) Electrically-induced tachycardia by atrial pacing carried out with a Medtronic 5840 external pacemaker. Atrial capture of the ventricle was complete except for occasional sinus capture. Pacing achieved an approximately 50 percent increase over basal heart rate. (2) Isoproterenol, 2 to 8 μg/min, was infused through a superficial vein in the opposite arm and continued for at least 5 minutes before mea-

TABLE II

Myocardial Lactate and Pyruvate Balance in Response to Stress Before and After Transfusion

	Before Transfusion							After Transfusion						
	L_A	L_{A-V}	$(A-V/A)_L$	P_A	P_{A-V}	L/P_A	L/P_{CS}	L_A	L_{A-V}	$(A-V/A)_L$	P_A	P_{A-V}	L/P_A	L/P_{CS}
Mean														
R	0.57	0.06	5.9	0.07	0.00	8.9	8.2	0.78	0.34	22.9	0.08	0.02	11.2	13.2
Tachy	0.60	0.06	7.9	0.08	0.02	9.3	11.6	0.81	0.24	34.3	0.08	0.02	10.9	10.0
P value														
R, tachy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mean														
R	0.53	−0.01	−1.2	0.06	0.02	8.9	13.4	0.73	0.17	22.0	0.06	0.01	12.4	8.7
Iso	0.90	−0.27	−29.9	0.08	−0.01	10.9	13.4	1.18	0.10	5.0	0.08	0.00	27.3	14.7
P value														
R, iso	<0.05	<0.02	<0.05	NS	NS	NS	NS	NS	NS	<0.05	NS	NS	NS	NS
Mean														
R	1.09	0.02	4.5	0.08	−0.02	15.3	10.9	0.70	0.11	9.6	0.09	0.01	30.6	11.9
E	2.46	0.06	2.4	0.12	0.03	21.8	26.3	2.78	0.57	19.2	0.13	0.02	33.6	25.9
P value														
R, E	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

$(A-V/A)_L$ = extraction coefficient for lactate (%); E = exercise; Iso = isoproterenol; L_A = arterial lactate (mm/liter); L_{A-V} = coronary arteriovenous difference for lactate (mm/liter); L/P_A = lactate/pyruvate concentration in arterial blood; L/P_{CS} = lactate/pyruvate concentration ratio in coronary sinus blood; P_A = arterial pyruvate (mm/liter); P_{A-V} = coronary arteriovenous difference for pyruvate (mm/liter).

surements were made. An increase in heart rate of 30 to 50 percent above the basal rate, with narrowing of the arterial pulse contour, was the usual end-point. (3) Exercise was performed on a bicycle ergometer in the supine position by 4 of the 6 patients and was continued for 5 minutes before measurements were begun.

During each physiologic state, phasic and mean (electronically derived) arterial pressures were recorded, cardiac output was measured and arterial and coronary sinus blood samples were obtained for lactate and pyruvate analysis. Measurements were made at least 5 minutes after achievement of a stable hemodynamic state, as judged by stabilization of heart rate and blood pressure. A control resting state preceded each stress intervention; 15 minutes were allowed between the end of each test period and the next control period. Lead II of the electrocardiogram was constantly recorded. Blood for oxygen analysis was not collected because of the concern over excessive phlebotomies.

All the patients received a transfusion of 500 ml of fresh packed red cells over 90 minutes, and the entire

TABLE III

Hemodynamic Response to Tachycardia, Isoproterenol and Exercise Stresses Before and After Transfusion

	Before Transfusion				After Transfusion			
	HR	CI	PTM	SER	HR	CI	PTM	SER
Mean								
R	92	4.0	2875	152	96	3.5	3587	133
Tachy	148	3.8	3704	109	145	3.5	4051	116
P value								
R, tachy	<0.02	NS	<0.02	<0.05	<0.01	NS	<0.05	<0.02
Mean								
R	100	4.1	3176	143	93	3.6	3572	140
Iso	133	5.3	2766	199	139	6.7	3720	179
P value								
R, Iso	<0.01	<0.02	NS	<0.05	<0.01	<0.01	NS	<0.05
Mean								
R	96	3.9	1895	150	99	3.0	3733	119
E	129	5.8	4129	176	127	5.3	4905	135
P value								
R, E	NS	<0.02	NS	NS	NS	...	NS	...

CI = cardiac index (liters/min per m^2); HR = heart rate (beat/min); PTM = pressure time per minute (mm Hg sec/min); SER = systolic ejection rate (ml/sec per m^2). Other abbreviations as in Table II.

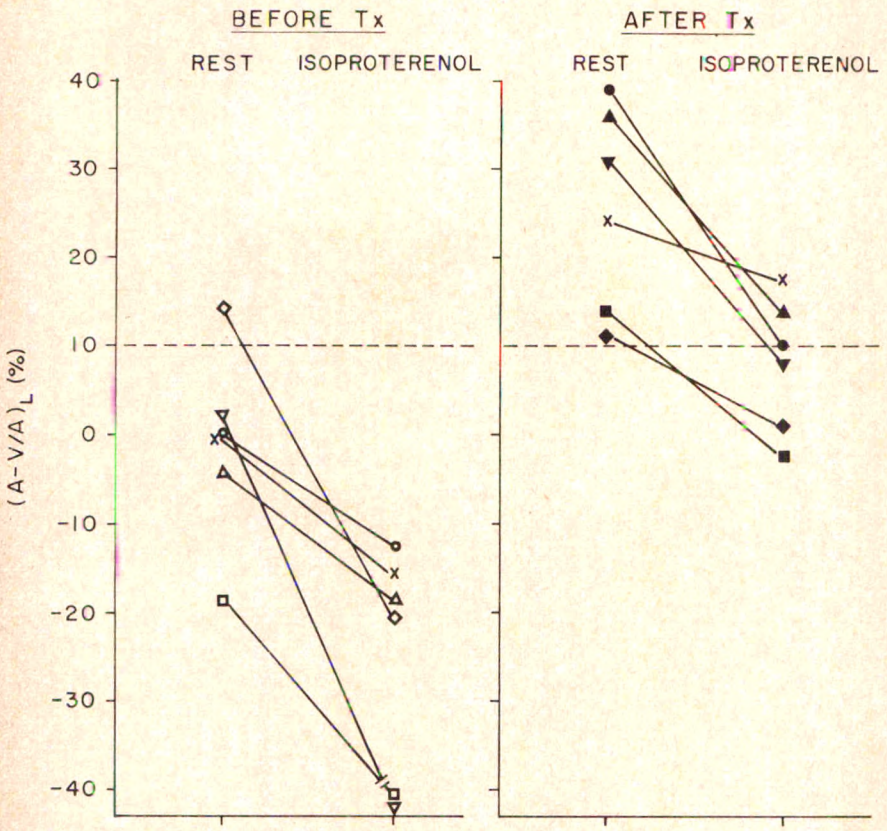

Figure 1. Myocardial lactate extraction percentage, at rest and during isoproterenol infusion. Open symbols, before transfusion (Tx); closed symbols, after transfusion. The dashed horizontal line at 10 percent extraction represents the lower limit of normal extraction.[2]

protocol was repeated. The rate of the induced electrical tachycardia was maintained as close as possible to that of the state before transfusion, as was the infusion rate of isoproterenol.

In addition to the measured hemodynamic parameters, systolic ejection rate index (stroke index divided by systolic ejection period) and pressure-time per minute (arterial systolic mean pressure times systolic ejection period times heart rate) were calculated using at least 6 beats in each experimental period. These indexes are related, albeit indirectly, to the energy requirements of the heart.[10,11]

Data were analyzed for paired differences using Student's t test.[12]

Results

Mean lactate and pyruvate balance data are given in Table II, and the mean hemodynamic changes produced by the 3 stresses in Table III.

Hematocrit: The average hematocrit before transfusion was 17.1 percent (range 14 to 21) and after transfusion was 24.5 percent (range 21 to 28).

The arterial lactate concentration at rest increased after transfusion in 8 of 15 experimental periods. The lactate concentration of the transfused blood averaged 8.0 mM/liter in 3 test samples.

Extraction Coefficient for Lactate

Isoproterenol (Fig. 1): During the control period before transfusion, the mean extraction coefficient for lactate $(A–V/A)_L$ was −1.2 percent (range 14.3 to −18.9 percent). In 5 of the 6 studies, the extraction was less than 10 percent. During infusion of isoproterenol, lactate was produced by the heart in all patients, the extraction coefficient ranging from −12.9 to −76.5 percent (mean −29.9 percent). This increase in lactate production was statistically significant ($P < 0.05$). After transfusion, there was marked improvement, with increase in the lactate extraction in all 6 subjects. At rest the mean extraction coefficient was now 22.0 percent (range 11.0 to 39.3 percent), and no patient produced lactate. Isoproterenol infusion given at the same rate as before transfusion produced a similar hemodynamic response, increasing the heart rate an average of 33 beats/min before and 46 beats/min after transfusion. The mean lactate extraction decreased to 5.0 percent (17.5 to −2.6 percent), but only 1 patient produced lactate.

Arterial lactate increased significantly ($P < 0.05$) from 0.53 mM/liter at rest to 0.90 mM/liter during isoproterenol infusion. A similar absolute rise after transfusion, 0.73 to 1.18 mM/liter, was not statistically significant.

Tachycardia: Before transfusion, during the resting period, the mean myocardial lactate extraction coefficient was −5.9 percent. Lactate extraction was greater than 10 percent in 3 of 6 patients, whereas 2 patients produced lactate. With electrically induced tachycardia sufficient to raise the

heart rate by an average of 56 beats/min, the extraction increased in 4 patients, although 2 patients produced lactate. The heart was paced at a similar rate after transfusion in 5 patients. The mean extraction coefficient increased slightly from 22.9 percent at rest to 34.3 percent during tachycardia. This increase represented a change to normal extraction in 4 of the 5 patients compared to the change with tachycardia before transfusion. However, these results were not statistically significant. Arterial lactate concentration was unchanged during tachycardia, compared to the concentration in the prior resting period (0.57 to 0.60 mM/liter).

Exercise: Before transfusion, the mean myocardial lactate extraction coefficient at rest was 4.5 percent (8.7 to −1.0 percent); 1 patient produced lactate. Exercise was sufficient to raise the heart rate an average of 33 beats/min and the mean cardiac index from 3.0 to 5.3 liters/min per m^2. The mean extraction coefficient was not significantly changed at 2.4 percent (range 20.8 to −22.4 percent). Two patients increased their myocardial lactate extraction, 1 remained unchanged, and 1 patient produced lactate. Exercise after transfusion was performed in 3 patients: the mean extraction coefficient increased from 9.6 percent in the control state to 19.2 percent during exercise.

Lactate/Pyruvate Ratios

Isoproterenol: The mean transmyocardial lactate/pyruvate ratio increased from 8.9 to 13.4 during the resting period, and from 10.9 to 13.3 during isoproterenol infusion. However, these changes were not statistically significant ($P < 0.20$).

Tachycardia: The lactate/pyruvate ratio (Fig. 2) was unchanged from arterial to coronary sinus blood in the resting state (8.9 to 8.2, respectively) and did not increase significantly across the heart during tachycardia (7.9 to 11.6).

Exercise: Lactate/pyruvate ratios did not change in predictable fashion between arterial and coronary sinus blood in either resting or exercise periods, whereas the mean arterial lactate increased significantly ($P < 0.05$) from 1.09 to 2.46 mM/liter during exercise.

The change in lactate/pyruvate ratio from arterial to coronary sinus blood was not significant in any experimental subgroup, presumably because the number of studies may have been too few. When all groups were combined, the change in lactate/pyruvate ratio in response to stress increased significantly ($P < 0.01$) before transfusion but not after transfusion. The transmyocardial increase in lactate/pyruvate ratio during stress was significant ($P < 0.025$) also when only the tachycardia

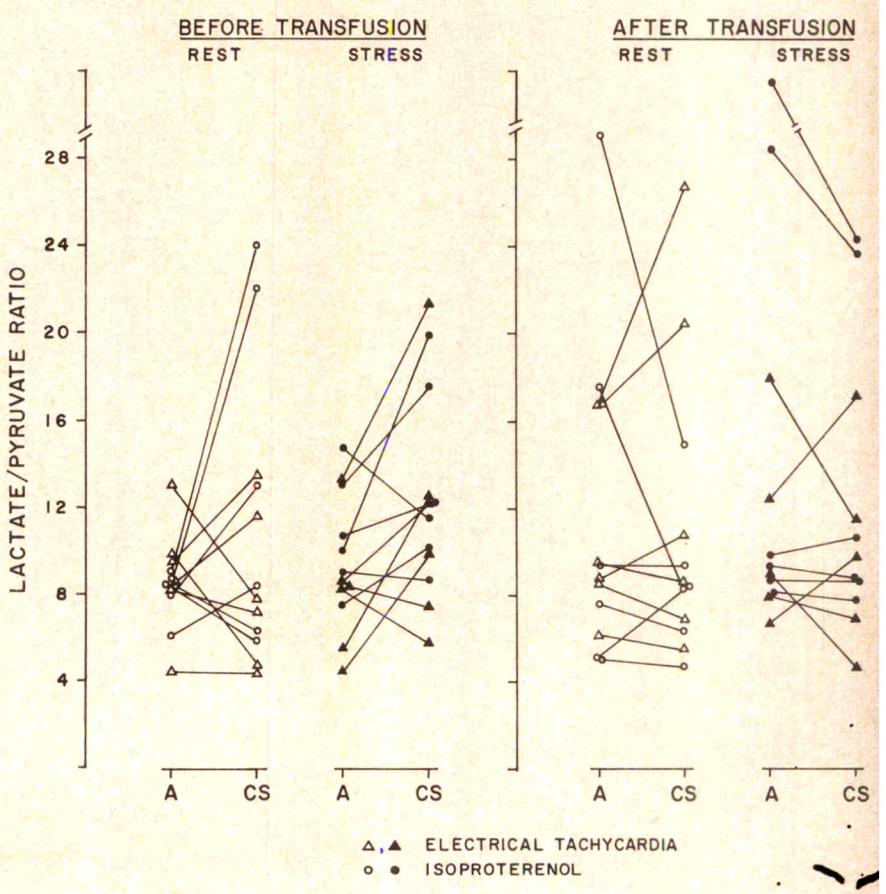

Figure 2. Lactate/pyruvate (L/P) ratios during stress induced by electrically-induced tachycardia or isoproterenol infusion, before and after transfusion. The rise in the L/P ratio from artery (A) to coronary sinus (CS) during stress before transfusion was statistically significant compared to the resting state ($P < 0.025$). Triangles = tachycardia; circles = isoproterenol; open symbols = resting state; closed symbols = during stress.

and isoproterenol stress studies were grouped (Fig. 2).

Hemodynamics (Table III)

The findings were consistent with previous studies of anemia.[13,14] Before transfusion, the mean cardiac index was elevated at 4.1 liters/min per m^2 and increased further to 5.8 and 5.3 liters/min per m^2 during exercise and isoproterenol infusion, respectively, but did not change significantly with electrically-induced tachycardia. After transfusion the resting cardiac index returned to the normal range except for 1 patient in whom it remained increased.

The mean pressure time per minute increased during exercise and electrically induced tachycardia by 117 and 29 percent, respectively, before transfusion, and by 31 and 13 percent respectively after transfusion. These smaller percentage increases in pressure time per minute after transfusion were, however, associated with greater absolute values for this index than before transfusion. Therefore, the stress induced was at least as great after as before transfusion.

The mean systolic ejection rate increased with exercise before and after transfusion, but the number of studies was too small for statistical significance. During electrical tachycardia, mean systolic ejection rate decreased significantly before ($P < 0.05$) and after ($P < 0.02$) transfusion. During isoproterenol infusion the systolic ejection rate increased by 24 percent before transfusion and 28 percent after transfusion. This effect of isoproterenol was accompanied by insignificant changes in the pressure time per minute before and after transfusion.

Discussion

Normal myocardium depends almost exclusively for energy production on aerobic metabolism of a variety of substrates by mitochondria, with consumption of oxygen. Several methods of demonstrating anaerobiosis have been proposed, including transmyocardial blood lactate/pyruvate ratios,[15] excess lactate[16] and myocardial lactate production.[1] It may be difficult to maintain a constant arterial lactate concentration, which is required to permit interpretation of change in lactate/pyruvate ratios.[3] Furthermore, studies of lactate and pyruvate kinetics in isolated perfused hearts have demonstrated a difference in the relative efflux rates of these substances.[17] Theoretical and practical difficulties render the excess lactate concept tenuous.[2,18,19] Thus, myocardial lactate production is probably the most practical means available for estimating myocardial anaerobiosis in vivo, especially when arterial lactate concentrations are altered.[1] Neill and Huckabee[7] have shown that myocardial lactate production is linearly related to anaerobic heat production. This is true whether or not hypoxia is present, as demonstrated by increases in coronary lactate/pyruvate ratio.

Normally, oxygen uptake by heart muscle is provided by the extraction of oxygen at a given level of coronary blood flow. Increased demand for oxygen is normally met by increases in coronary flow, rather than by increased extraction.[20] The limits of this flow-regulated system for oxygen delivery to the myocardium have not been explored. Anaerobic metabolism of the myocardium has been demonstrated previously in man, generally under conditions in which coronary flow was limited. Krasnow and Gorlin[2] first demonstrated a high incidence of abnormal lactate metabolism (less than 10 percent extraction) in patients with coronary insufficiency compared with subjects who had heart disease but not angina pectoris. An abnormal lactate response to exercise or isoproterenol[2] has been correlated with the presence of coronary artery disease proved angiographically.[5,6] Neill[3] showed that electrically induced tachycardia or moderate systemic hypoxia[21] in subjects with coronary artery disease produced a rise in the lactate/pyruvate ratio of coronary sinus blood compared to arterial blood. He interpreted these changes as indicative of myocardial tissue hypoxia.

Anaerobiosis without ischemic heart disease: It is highly unlikely that the observed abnormalities in lactate metabolism in these patients were caused by obstructive coronary heart disease. The patients were under age 31 years and had no chest pain suggestive of angina pectoris or electrocardiographic evidence of myocardial infarction. There was minimal or no hypertension, and heart size by X-ray examination was normal. One patient died of pulmonary hemorrhage 2 weeks after the study, and had a normal heart and coronary arteries at autopsy.

It is therefore concluded that patients with normal coronary vessels and stable, normal cardiac function utilized anaerobic metabolism as an adjustment to inadequate oxygenation due to the anemia of uremia. There was evidence of subnormal or reversed extraction of lactate at rest and evidence of definite anaerobic metabolism during the stress of isoproterenol in all 6 subjects. The results with exercise or tachycardia were more variable, although myocardial lactate was produced on some occasions with these stresses also. The change in lactate/pyruvate ratio from arterial to coronary venous blood was not significant in the control state but increased significantly ($P < 0.01$) during stress (Fig. 2). After transfusion, there was no significant change in lactate/pyruvate ratio during stress. The rise in lactate/pyruvate ratio with stress suggests that the anaerobic heat associated with lactate production was accompanied by tissue hypoxia rather than aerobic glycolysis.[15]

Cardiac performance: When hypoxic stress has produced anaerobiosis in experimental animals, the stress has usually been extreme[7,22,23] and asso-

ciated with hemodynamic evidence of left ventricular failure.[24,26] Similarly, in subjects with coronary artery disease an increase in left ventricular end-diastolic pressure occurs as stress induces angina.[27] In our subjects, gross cardiac performance was normal despite evidence of resting or stress-induced anaerobiosis, or both. Cardiac index and systolic ejection rate were high at rest and increased normally with exercise.[28] The heart was not enlarged and wedge pressure was normal at rest in the 2 patients in whom it was measured. It is therefore likely that the chronic anemic state did not lead to gross uncompensated cardiac dysfunction although more detailed ventricular hemodynamics would be necessary to prove this point.

Physiologic correlation: The question remains whether the biochemical abnormality demonstrated in the present anemic subjects has any physiologic importance in these well-rehabilitated uremic patients. These patients were part of a larger group of 11 young anemic subjects with renal failure who performed a double Master exercise test, of whom 6 had abnormal results, according to the criteria of Mattingly.[29] Three of these patients with abnormal test findings repeated the test at a higher hematocrit level, and all findings returned to normal (unpublished observation). In no instance was chest pain associated with the electrical abnormality, although one can assume that the lactate balance had become negative in some of these patients.[30] Thus, it is likely that the myocardial lactate production induced in the laboratory by isoproterenol is paralleled by the electrophysiologic abnormalities of exercise as exemplified by the abnormal results of the Master exercise test.

Role of chronic uremia: The significance of the uremic state in the genesis of the anaerobic cardiac metabolism is not certain, although the improvement in lactate metabolism after transfusion would suggest that this factor is not a critical determinant. It was not possible to study a comparable control group of young anemic subjects without uremia. Studies in vitro of the effect of uremic sera on mitochondrial metabolism give conflicting results.[31–33] No elevation of blood lactate, pyruvate or lactate/pyruvate ratio has been demonstrated in chronic uremia,[34–36] and changes in blood levels of Kreb cycle metabolites were variable. In any event, the major finding in this study is that anaerobic metabolism by the heart may occur under conditions other than ischemia. Uremia as a potential factor added to the anemia would not negate this conclusion.

Isoproterenol versus tachycardia stress: Isoproterenol in moderate dosage induced myocardial lactate production consistently in these patients, whereas tachycardia and exercise were less useful. Baker and co-workers[37] noted more consistent evidence for anaerobiosis with tachycardia compared with isoproterenol when subjects with coronary artery disease were studied. In our study, myocardial energy demand as reflected by changes in pressure time and systolic ejection rate indexes were balanced during electrical tachycardia, that is, pressure time per minute increased by 32 percent and systolic ejection rate decreased by 28 percent. During isoproterenol infusion, the decrease in pressure time per minute was small, 13 percent, whereas systolic ejection rate increased markedly, 39 percent. Although the distribution of energy requirement between pressure generated and fiber velocity is not known, the energy demand during isoproterenol infusion in this study may have been greater than during tachycardia. One could speculate that in our patients the coronary vasculature had already approached the limit of physiologic vasodilatation; further dilatation secondary to beta adrenergic stimulation may therefore have been ineffective in meeting the inotropic load imposed by the catecholamine. In patients with coronary artery disease, the inotropic stress of isoproterenol may be partly offset by vasodilatation with an increase in coronary flow to marginally perfused myocardium. Also, anemic hearts are probably more uniform in production of lactate, whereas regional lactate production in coronary artery disease may be obscured by the isoproterenol-induced increase in flow to the nonobstructed areas.

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The Relation Between Myocardial ^{3}H-Digoxin Concentration and Its Hemodynamic Effects

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The relation between myocardial digoxin concentration and its hemodynamic effects in the same animal was studied in 23 open chest anesthetized dogs with intact circulations given digoxin, 0.08 mg/kg body weight (0.04 mg/kg ^{3}H-digoxin) intravenously. During the succeeding 5 to 240 minutes, hemodynamic measurements were made, and plasma and myocardial ^{3}H-digoxin concentrations were determined. At 5 minutes there was no change in left ventricular dp/dt or right ventricular contractile force, but at 15 minutes 33 to 66 percent of peak positive inotropic effect was observed. Peak effect occurred at 60 minutes for the left ventricle, and at 180 minutes for the right ventricle. In contrast, myocardial ^{3}H-digoxin concentration increased more rapidly with 50 percent of maximal ventricular concentration present at 5 minutes and near maximal concentration reached at 15 minutes. Thus, the hemodynamic effects of digoxin lagged behind the myocardial ^{3}H-digoxin concentration. This finding suggested that the total myocardial ^{3}H-digoxin concentration was not the only determinant of the rate of onset and development of the inotropic effects of digoxin. Other possible determinants are discussed. An additional observation was the difference in distribution of ^{3}H-digoxin in the various parts of the heart and skeletal muscle. Right ventricular ^{3}H-digoxin concentrations were 78.2 percent, atrial concentrations 44.9 percent, and skeletal muscle concentrations 12.9 percent of left ventricular concentrations, which were about the same as those of the interventricular septum. One possible explanation offered for this observation is differences in blood flow to the various parts of the myocardium.

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In an attempt to understand the complex circulatory action of the cardiac glycosides, recent studies have described the kinetics of the absorption, tissue distribution, metabolism and excretion of radioactive digitalis preparations in man and dogs,[1–8] and Doherty has recently reviewed this subject.[9] None of these studies have attempted to correlate the relation between myocardial ^{3}H-digoxin concentration and its hemodynamic effects. Although experiments utilizing isolated preparations of animal hearts have examined this relation,[10–14] the results of these studies are difficult to apply to the intact animal or man. Therefore, the experiments described in this paper were designed to investigate the relation between the myocardial concentration of ^{3}H-digoxin and its hemodynamic effects in the same dogs with an intact circulatory system.

Methods

Twenty-three mongrel dogs (9 to 15 kg) were anesthetized with a mixture of alpha-chloralose and urethane, 85 and 625 mg/kg body weight, respectively. Supplemental anesthetic was administered when corneal reflexes were noted. The animals were intubated with a cuffed endotracheal tube and ventilated with a Harvard respirator supplying humidified room air. Arterial blood samples were analyzed frequently, utilizing a model AME-1 Astrup microapparatus, and the tidal volume and respiratory rate were adjusted to maintain blood pH at 7.40 ± 0.05 and pO_2 above 80 mm Hg.

Physiologic Measurements

After the chest was opened through a midline sternotomy, instruments were inserted for physiologic measurements. Pressures were measured in the descending aorta through a PE-260 catheter introduced by way of the left femoral artery. Left ventricular pressure was monitored by means of a 35 cm stiff-wall PE-260 catheter introduced into the left ventricle by way of the left carotid artery. The aortic and left ventricular catheters were connected to Statham P23Db transducers, and pressures were recorded on a multichannel Beckman Model R direct-writing oscillograph. The rate of change of the left ventricular pressure (dp/dt) was recorded directly from the left ventricular pressure curve by means of a resistance-capacitance (R-C) differentiator. The manometer catheter system was calibrated by a transient analysis described by Hansen[15] and had a natural frequency of 20 cycles/sec and a critical damping fraction of 0.16, which is adequate to record accurate intracardiac pressure measurements.[16] The frequency response of the R-C differentiator to a triangular wave was determined to be linear and flat to 30 cycles/sec.

Pressures were measured in the right atrium by means of a PE-260 catheter introduced by way of the left femoral vein. Left atrial pressure was recorded through a PE-260 flange-tipped catheter introduced directly into the left atrium through a stab wound in the left atrial appendage. The atrial catheters were connected to a saline manometer, and direct readings were made in millimeters of water and converted to millimeters of mercury pressure. A catheter was placed into the inferior vena cava by way of the right femoral vein for infusion of fluids and ^{3}H-digoxin.

Cardiac contractile force was measured with a Honeywell strain gauge arch sutured to the anterior wall of the right ventricle and stretched to yield maximal tension readings. Mean aortic blood flow was measured with a gated sine wave electromagnetic flowmeter (Biotronex Laboratory, Silver Spring, Md.). The aortic flow probe was placed around the ascending aorta distal to the coronary arteries. Each aortic flow probe was calibrated using a flow simulator. Pacemaker electrodes were attached to the right atrium, and the heart was paced at a rate of 180 to 220/min with a Grass Model 54 stimulator. These rapid pacing rates were those necessary to obtain complete capture. Aortic and left ventricular pressures, left ventricular dp/dt, right ventricular contractile force, aortic flow and lead II of the electrocardiogram were recorded continuously on the Beckman Model R direct-writing oscillograph.

After instrumentation, the animals were volume-loaded with 8 ml/kg of 6 percent Dextran-70, and throughout the study were given supplemental amounts as necessary to maintain a constant left atrial pressure. Normal saline solution was also administered at a constant rate of 60 ml/hour by a Sigmamotor Model TM 204 infusion pump. Animals were allowed to stabilize for 1 hour before study. Nineteen dogs were given digoxin, 0.08 mg/kg, half of which was ^{3}H-digoxin (144 μc/mg),* intravenously over 30 seconds, and 4 dogs served as controls and did not receive digoxin. Physiologic measurements and heparinized blood samples were taken at 15, 30, 60, 120, 180 and 240 minutes. All dogs in the control group were sacrificed at 240 minutes.

After completing the study of dogs killed at 15, 60, 120 and 240 minutes, we studied another group of 4 dogs at 5 minutes after administration of digoxin, to define more clearly the relation between myocardial ^{3}H-digoxin concentration and the onset of its hemodynamic effects. The instruments and study procedures were as previously described.

Systemic vascular resistance was determined by dividing the mean aortic pressure by the cardiac output. Stroke volume was determined by dividing the mean cardiac output by the heart rate and is expressed in milliliters per beat.

Biochemical Analyses

The heart and skeletal muscle from the right hind limb were removed from each dog, blotted dry, and frozen. Quadruplicate samples of the left ventricle, interventricular septum, right ventricle, atria and skeletal muscle of each dog were weighed, then homogenized in a Virtis homogenizer using chloroform and ethanol. Tritiated digoxin was extracted by shaking with 20 percent ethanol in chloroform, and the mixture was then filtered. The supernatant was evaporated to dryness, and the residue taken up in 0.2 ml of absolute alcohol and then 10 ml of a counting solution, 3 g of 2.5-diphenyloxazole (POP) and 0.1 g dimethyl 1,4 bis-2(4-methyl-5-diphenyl-oxazolyl-benzene) (dimethyl POPOP) dissolved in 1 liter of toluene, was added. All samples were counted in a Packard Tri-Carb liquid scintillation spectrometer, at an efficiency of 35 percent, to accumulate at least 5,000 counts. Correction for quenching, which averaged less than 10 percent, was done by the addition of tritiated toluene. Previous studies in our laboratory indicated that additional extractions with chloroform-ethanol or use of alumina columns did not significantly affect the recovery of tritiated digoxin.

Extracts of myocardial tissue from animals sacrificed at 240 minutes were subjected to thin layer chromatography to determine whether the tritium measured was attached to digoxin or one of its metabolites. These extracts were prepared as discussed in the previous paragraph with the addition of nonradioactive digoxin, digoxigenin mono-digitoxiside, digoxigenin bis-digitoxoside, digoxigenin and dihydrodigoxigenin as carriers. They were spotted on Brinkman silica gel F-254, containing calcium sulfate as binder and an ultraviolet indicator. The chromatograms were developed 4 times to a height of 15 cm above the origin, using the ascending technique with methyl isobutyl

* Kindly supplied by Stanley T. Bloomfield, MD, of Burroughs Wellcome and Co., Inc., Tuckahoe, N. Y.

ketone, isopropyl ether and n-butanol in a ratio of 8:6:1. This procedure resulted in a clear-cut separation of digoxin from each of its metabolic products. The chromatographic plates were then sprayed with 20 percent p-toluenesulfonic acid in methanol and heated at 100C for 10 minutes before being scanned under ultraviolet light. The fluorescent spots were recovered from the plates by extraction of the glycosides with 95 percent ethanol. These extracts were placed into counting vials, evaporated to dryness, redissolved in 0.2 ml of absolute alcohol and, after addition of counting solution, were counted as previously described. The chromatograms of the extracts of myocardial tissue obtained from the 240 minute animals showed that over 90 percent of the radioactivity traveled with the nonradioactive carrier, digoxin. Therefore, "digoxin" hereafter refers to both digoxin and its metabolites.

Plasma levels of radioactive digoxin were determined by adding 1 ml of plasma to 10 ml of 95 percent ethanol and shaking the solution for 10 minutes. After centrifugation at 2,200 revolutions per minute for 10 minutes, the supernatant was transferred to counting vials. The precipitate was re-extracted with 95 percent ethanol, and the 2 supernatants were combined. The mixture was evaporated to dryness, and the residue was reconstituted with absolute alcohol. After the addition of counting solution, scintillation counting was performed. Further extraction with 95 percent ethanol did not affect recovery of ^{3}H-digoxin.

Plasma sodium and potassium levels were determined by flame photometry. Myocardial samples were wet-ashed in concentrated nitric acid until fully digested, diluted to volume, and then sodium and potassium content was measured by flame photometry. Plasma creatinine values were determined by autoanalyzer using a modification of the Folin-Wu method.[17] None of these indexes changed significantly during the study.

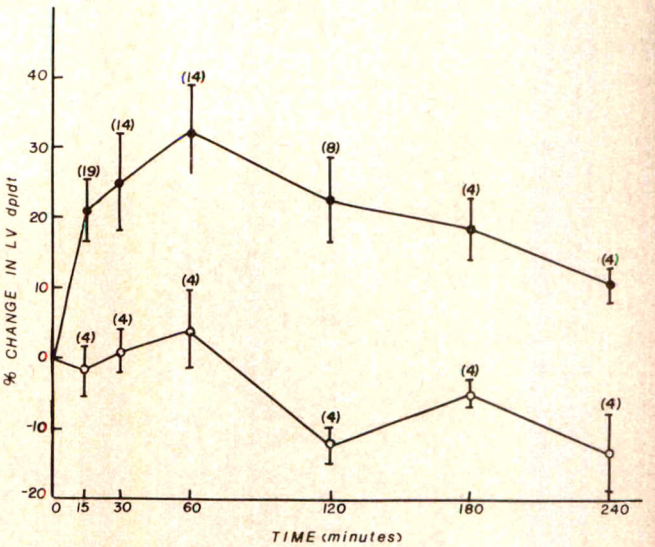

Figure 1. Percentage changes ± SEM of left ventricular (LV) dp/dt for control (open circle) and experimental (closed circle) groups. Numbers in parentheses represent the number of observations at each time.

Statistical Analyses

The hemodynamic and tritiated digoxin data were evaluated for statistical significance by using an IBM 36/50 computer programmed to calculate means and standard errors and to perform paired *t* test analysis. Each set of hemodynamic data obtained after administration of digoxin was compared to the set obtained just before administration (zero time) in the individual dogs; the absolute and percentage differences were calculated, and the statistical significance of the data was determined. The same analysis was performed for the 4 control animals. Tritiated digoxin data were analyzed using both paired and unpaired *t* tests.

TABLE I

Absolute Values of Left Ventricular dp/dt and Right Ventricular Contractile Force

	Experimental Group			Control Group		
Time (min)	no.*	LV dp/dt (mm Hg/sec ± SEM)	RVCF (units ± SEM)	no.*	LV dp/dt (mm Hg/sec ± SEM)	RVCF (units ± SEM)
0	19	6257 ± 493	14.8 ± 1.3	4	7175 ± 1816	13.3 ± 1.4
15	...	7350 ± 470‡	17.7 ± 1.6‡	...	7050 ± 1850	12.3 ± 1.7
	14	6128 ± 542	13.8 ± 1.3	...	...	...
30	...	7371 ± 495‡	16.5 ± 1.6‡	...	7250 ± 2034	12.3 ± 1.3
60	...	7786 ± 457‡¶	17.6 ± 1.8‡//	...	7500 ± 1977	12.8 ± 1.4
	8	6419 ± 759	14.4 ± 1.9	...	...	...
120	...	7684 ± 776‡	19.9 ± 3.3†	...	6275 ± 1643†//	11.8 ± 1.0
	4	5088 ± 208	9.5 ± 1.0	...	...	...
180	...	6008 ± 172†	13.5 ± 0.6†	...	6787 ± 1705	12.5 ± 1.3
240	...	5593 ± 131†	12.8 ± 0.5	...	6225 ± 1676	12.8 ± 1.4

* Number of dogs studied at zero time which were used in performing a paired t test for the succeeding time intervals. † P <0.05 significance compared to zero time; ‡ P <0.01 significance compared to zero time; // P <0.05 significance compared to 15 minutes; ¶ P <0.01 significance compared to 15 minutes.

LV = left ventricular; RVCF = right ventricular contractile force.

TABLE II

Left Ventricular, Aortic and Right Atrial Pressure Measurements (mm Hg ± SEM)

Time (min)	Experimental Group						Control Group					
	no.*	LV S	Ao S	Ao D	Ao M	RA M	no.*	LV S	Ao S	Ao D	Ao M	RA M
0	19	156 ± 5	154 ± 6	103 ± 4	121 ± 4	4.2 ± 0.2	4	167 ± 17	150 ± 11	95 ± 11	115 ± 11	4.5 ± 0.3
15	...	165 ± 4†	159 ± 5†	107 ± 4	125 ± 4	3.9 ± 0.2†	...	163 ± 15	145 ± 12	98 ± 13	113 ± 13	4.5 ± 0.2
	14	157 ± 6	155 ± 6	104 ± 4	122 ± 5	4.2 ± 0.3	...	...	...	...	...	...
30	...	164 ± 5	160 ± 6	107 ± 4	124 ± 5	4.1 ± 0.3	...	166 ± 18	146 ± 16	94 ± 12	116 ± 13	4.7 ± 0.3
60	...	159 ± 5	159 ± 5	102 ± 4	120 ± 4	4.3 ± 0.3	...	169 ± 15	154 ± 14	99 ± 11	199 ± 11	4.7 ± 0.3
	8	154 ± 4	156 ± 6	105 ± 5	122 ± 5	4.6 ± 0.4	...	...	...	...	...	...
120	...	160 ± 5	160 ± 6	101 ± 5	119 ± 5	5.1 ± 0.4†	...	158 ± 16	149 ± 19	101 ± 13	121 ± 13	4.7 ± 0.3
	4	153 ± 9	145 ± 8	103 ± 9	120 ± 9	3.8 ± 0.3	...	...	...	...	...	...
180	...	162 ± 7	147 ± 4	98 ± 8	119 ± 9	4.6 ± 0.7	...	156 ± 18	151 ± 14	98 ± 10	118 ± 11	4.6 ± 0.2
240	...	159 ± 6	145 ± 10	99 ± 10	116 ± 9	4.9 ± 0.5†	...	150 ± 15	147 ± 11	94 ± 8	111 ± 7	4.5 ± 0.2

* Number of dogs studied at zero time which were used in performing a paired t test for the succeeding time intervals; † $P < 0.05$ significance compared to zero time; ‡ $P < 0.01$ significance compared to zero time.

Ao = aortic; D = diastolic; LV = left ventricular; M = mean; RA = right atrial; S = systolic.

Results

Hemodynamic data: The absolute values for left ventricular dp/dt are presented in Table I, and the percentage changes of dp/dt are shown in Figure 1. In the experimental group, there was a significant increase in dp/dt at 15 minutes ($P < 0.01$) and throughout the 240 minutes after administration of digoxin; in the control group, left ventricular dp/dt was unchanged during the first 60 minutes and then gradually decreased during the remainder of the experiment. The percentage changes from zero time in the left ventricular dp/dt of the experimental group were +21.1 ± 4.4 percent at 15 minutes, +32.6 ± 6.3 percent at 60 minutes, +22.3 ± 6.0 percent at 120 minutes and +10.2 ± 2.3 percent at 240 minutes. In the control group, left ventricular dp/dt percentage changes from zero time were not significantly different at 15 and 60 minutes (−2.0 ± 3.5 percent and +3.9 ± 5.5 percent, respectively) but were slightly lower at 120 and 240 minutes (−12.8 ± 2.5 percent and −13.6 ± 5.5 percent, respectively). At 60 minutes the left ventricular dp/dt of the experimental group was significantly higher than at 15 minutes ($P < 0.01$).

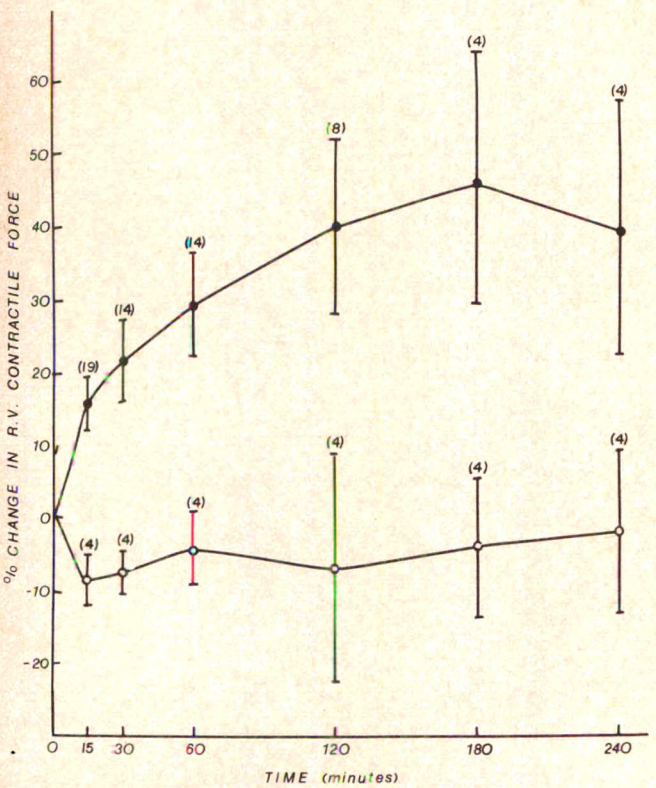

Figure 2. Percentage changes ± SEM of right ventricular (R.V.) contractile force for control (open circle) and experimental (closed circle) groups. Numbers in parentheses represent the number of observations at each time.

The absolute values for right ventricular contractile force are shown in Figure 2. It was significantly increased in the dogs that received digoxin but essentially unchanged in control animals. The percentage changes from zero time in the experimental group were +15.9 ± 3.3 percent at 15 minutes, +29.3 ± 6.9 percent at 60 minutes, +40.1 ± 12.0 percent at 120 minutes and +39.4 ± 17.6 percent at 240 minutes. At 60 minutes, right ventricular contractile force of the experimental group was statistically higher than at 15 minutes ($P < 0.02$). At 120 and 240 minutes, the percentage changes were 2½ times higher than at 15 minutes.

Aortic and left ventricular pressure measurements are presented in Table II. These remained unchanged in both the experimental and control groups, except for a slight rise in values for aortic systolic and left ventricular pressure at 15 minutes in the experimental group. Right atrial pres-

TABLE III

Cardiac Output, Stroke Volume and Systemic Vascular Resistance

Time (min)	Experimental Group				Control Group			
	no.*	CO	SV	SVR	no.*	CO	SV	SVR
0	19	1417 ± 80	7.3 ± 0.5	89 ± 5	4	1781 ± 371	8.5 ± 1.5	79 ± 25
15	...	1378 ± 77	6.9 ± 0.5	90 ± 7	...	1675 ± 295	8.1 ± 1.3	79 ± 24
	14	1392 ± 104	7.2 ± 0.6	93 ± 6	...	...	...	...
30	...	1311 ± 95†	6.8 ± 0.5†	102 ± 8†	...	1840 ± 371	8.8 ± 1.6	77 ± 24
60	...	1233 ± 97†	6.4 ± 0.5†	108 ± 12†	...	1821 ± 343	8.7 ± 1.4	77 ± 21
	8	1420 ± 113	7.3 ± 0.6	90 ± 8	...	...	...	...
120	...	1229 ± 131‡	6.3 ± 0.7‡	105 ± 13†	...	1611 ± 310	7.6 ± 1.2	86 ± 20
	4	1471 ± 150	7.9 ± 0.9	82 ± 5	...	...	...	...
180	...	1187 ± 157‡	6.4 ± 0.9‡	107 ± 14	...	1681 ± 277	8.1 ± 1.2	80 ± 22
240	...	1164 ± 171†	6.2 ± 0.9†	104 ± 14	...	1628 ± 196	7.9 ± 0.9†	74 ± 15

* Number of dogs studied at zero time which were used in performing a paired t test for the succeeding time intervals; † $P < 0.05$ significance compared to zero time; ‡ $P < 0.01$ significance compared to zero time.

CO = cardiac output (cc/min ± SEM); SV = stroke volume (cc/beat ± SEM); SVR = systemic vascular resistance (units ± SEM).

sure was unchanged in the control group, but was slightly lower at 15 minutes and slightly higher at 120 to 240 minutes in dogs in the experimental group.

Cardiac output, stroke volume and systemic vascular resistance data are shown in Table III. Cardiac output decreased significantly in the experimental group: −5.6 ± 2.2 percent at 30 minutes, −11.4 ± 3.9 percent at 60 minutes, −14.4 ± 3.7 percent at 120 minutes and −21.7 ± 4.8 percent at 240 minutes. The cardiac output of the control group decreased slightly over the same period of time. Since the heart rate was kept constant in each animal by right atrial pacing, the stroke volume reflects the same magnitude and direction of change as the cardiac output data in both experimental and control groups. In the experimental group, systemic vascular resistance increased +9.1 ± 3.1 percent at 30 minutes, +14.6 ± 5.5 percent at 60 minutes, +14.9 ± 5.8 percent at 120 minutes and +25.4 ± 10.9 percent at 240 minutes; in the control group it did not change significantly.

In the 4 dogs studied at 5 minutes after administration of digoxin there were no significant changes in left ventricular dp/dt, right ventricular contractile force, left ventricular systolic pressure, aortic pressure, mean right atrial pressure, cardiac output, stroke volume and systemic vascular resistance (Table IV). Thus, the onset of the circulatory effects of digoxin occurred between 5 and 15 minutes.

Tritiated digoxin data: The tissue ^{3}H-digoxin concentrations at each sacrifice time are presented in Figure 3. The ^{3}H-digoxin concentrations in specimens of the left ventricle interventricular septum, right ventricle, and atria at 15, 60, 120 and 240 minutes were significantly higher than at 5 minutes ($P < 0.01$ for left ventricle, interventricular septum and right ventricle; $P < 0.05$ for the atria). However, there were no significant differences among the corresponding specimens at 15, 60, 120 and 240 minutes. Thus, after digoxin administration, the ^{3}H-digoxin concentrations in the left ventricle increased to 55 percent, in the interventricular septum to 50 percent, in the right ventricle to 51 percent, and in the atria to 63 percent of their maximal concentrations within 5 minutes; they were near maximal at 15 minutes

TABLE IV

Hemodynamic Measurements in 4 Dogs Studied at 5 Minutes

Time (min)	no.*	LV dp/dt	RVCF	Pressures (mm Hg ± SEM)					CO	SV	SVR
				LV S	Ao S	Ao D	Ao M	RA M			
0	4	9461 ± 1240	16.8 ± 3.2	163 ± 11	165 ± 10	108 ± 3	125 ± 5	3.8 ± 0.2	1452 ± 139	7.0 ± 0.8	89 ± 9
5	...	9600 ± 920	17.5 ± 3.6	171 ± 10	160 ± 9	100 ± 4	121 ± 3	3.9 ± 0.3	1481 ± 147	7.1 ± 0.8	84 ± 7

* Number of dogs studied at zero time which were used in performing a paired t test for the succeeding time intervals.

Ao = aortic; CO = cardiac output (cc/min ± SEM); D = diastolic; LV dp/dt = left ventricular dp/dt (mm Hg/sec ± SEM); M = mean; RA = right atrial; RVCF = right ventricular contractile force (units ± SEM); S = systolic; SV = stroke volume (cc/beat ± SEM); SVR = systemic vascular resistance (units ± SEM).

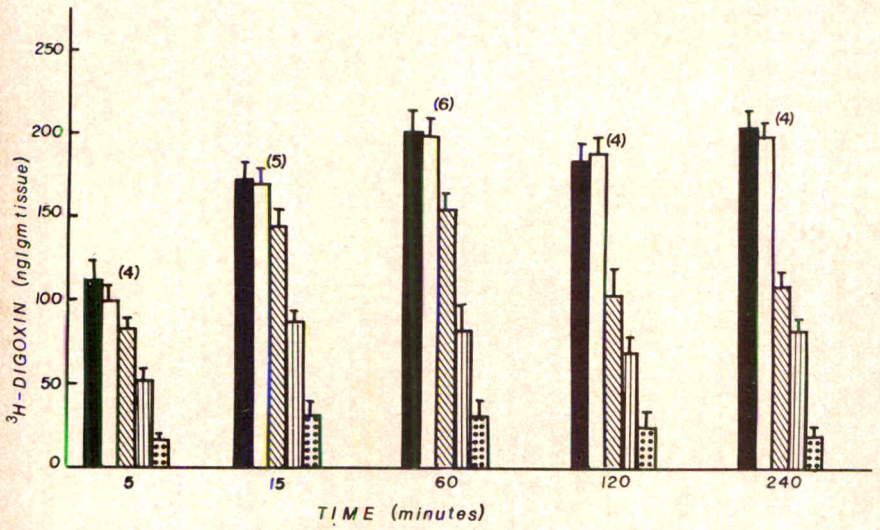

Figure 3. ^{3}H-digoxin concentration in ng/g wet weight ± SEM in the different cardiac chambers and skeletal muscle. Black bar = left ventricle; clear bar = interventricular septum; diagonally striped bar = right ventricle; vertically striped bar = atria; stippled bar = skeletal muscle. Numbers in parentheses represent the number of observations at each time period.

and did not change significantly throughout the remainder of the experiments.

There were significant differences in the ^{3}H-digoxin concentrations in the various parts of the heart and the skeletal muscle in each of the 23 experimental dogs. The concentrations were about equal and greatest in the left ventricle and interventricular septum. The concentrations of ^{3}H-digoxin in the right ventricle were significantly less than those of the left ventricle ($P < 0.001$). The ^{3}H-digoxin concentrations of the atria were significantly less than those of the right ventricle ($P < 0.001$), and the skeletal muscle ^{3}H-digoxin concentrations were significantly less than those of the atria ($P < 0.001$). Right ventricular concentrations were 78.2 percent, atrial concentrations 44.9 percent, and skeletal muscle concentrations 12.9 percent of left ventricular ^{3}H-digoxin concentrations.

Plasma ^{3}H-digoxin concentrations are shown in Figure 4. The plasma level showed a rapid decline in the first 120 minutes after administration of digoxin, but began to level off between 120 and 240 minutes.

Discussion

The hemodynamic results of this study are similar to others which have investigated the circulatory effects of the cardiac glycosides.[18–26] Left ventricular dp/dt, right ventricular contractile force and systemic vascular resistance increased, whereas cardiac output decreased and mean aortic pressure remained unchanged. Since left ventricular filling pressure, aortic diastolic pressure and heart rate were constant, the rise in left ventricular dp/dt must reflect a primary effect of digoxin on left ventricular contractility,[27–29] whereas the increase in right ventricular contractile force reflects a similar effect on the right ventricle.[30,31] No effect of digoxin was seen at 5 minutes, but at 15 minutes 33 to 66 percent of its peak inotropic effect was noted. Gold et al.[32] noted a similar onset of digoxin effect in slowing ventricular rate in patients with atrial fibrillation, whereas Weissler et al.[33] showed that systolic ejection time was shortened within 15 minutes after the intravenous administration of digoxin. The peak effect of digoxin occurred between 60 and 180 minutes, which is

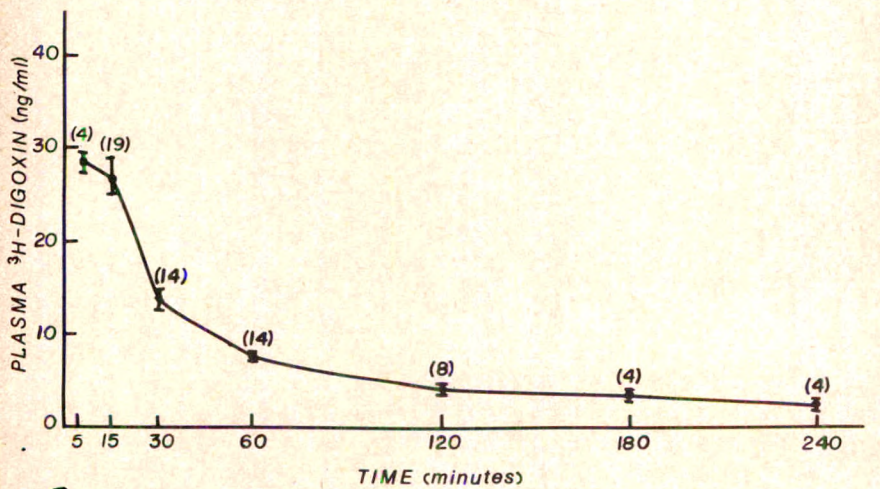

Figure 4. Plasma ^{3}H-digoxin concentration in ng/ml ± SEM. Numbers in parentheses represent the number of observations at each time period.

earlier than the peak effect of 6 hours noted by both Gold et al.[32] and Weissler et al.[33] However, their studies were in man, whereas our study was in open chest anesthetized dogs. Since hemodynamic studies in animals given no digitalis showed that our experimental preparation began to deteriorate slightly by 120 minutes, this might account for our earlier peak hemodynamic effects.

Cardiac intracellular uptake of ^{3}H-digoxin and positive inotropy: The initial hemodynamic effects of digoxin occurred after 5 minutes and before 15 minutes, whereas the maximal effects were not noted until 60 minutes for left ventricular dp/dt and 180 minutes for right ventricular contractile force. However, ventricular ^{3}H-digoxin concentration reached 50 percent of peak at 5 minutes and was near maximal at 15 minutes. Since myocardial ^{3}H-digoxin concentration greatly exceeded plasma ^{3}H-digoxin concentration at all times, myocardial ^{3}H-digoxin must reflect predominantly intracellular digoxin. Therefore, our data suggest that there is a lag between the intracellular uptake of ^{3}H-digoxin by the heart and the development of positive inotropy (Fig. 5). This is the first study utilizing animals with an intact circulation to correlate the uptake of ^{3}H-digoxin by the heart with its hemodynamic effects and to show the presence of a lag period between tissue uptake and physiologic effect. This lag period may be related to the contraction dependency of the positive inotropic effect of the cardiac glycosides, as shown by Moran.[34] He demonstrated in isolated rabbit left atria and in intact dogs that ouabain exerts its positive inotropic effect at a rate determined not by the time of exposure to the glycoside, but by the number of contractions that have occurred since exposure. He noted that the change in rabbit left atrial contractile force began 300 contractions after exposure to ouabain and reached maximum at approximately 3,000 contractions after ouabain exposure, corresponding to 1½ and 15 minutes in our dogs paced at an average heart rate of 200/min. In our study, at 15 minutes only the onset of inotropic effect was noted. The earlier appearance of positive inotropy in Moran's study might be explained by the fact that he used ouabain and studied rabbit left atria whereas we used digoxin in an intact dog. Roth-Schecter et al.[14] used quiescent and contracting guinea pig atria and showed that digoxin had a greater inotropic effect on the contracting atria, although there was no difference in ^{3}H-digoxin concentration between the washed quiescent and contracting atria.

Other possible determinants of digoxin inotropy: Thus, both in vitro and in vivo, the inotropic effect of digoxin is not determined by total myocardial ^{3}H-digoxin concentration alone, but may be partially related to the interaction of digoxin with a contraction-dependent process or

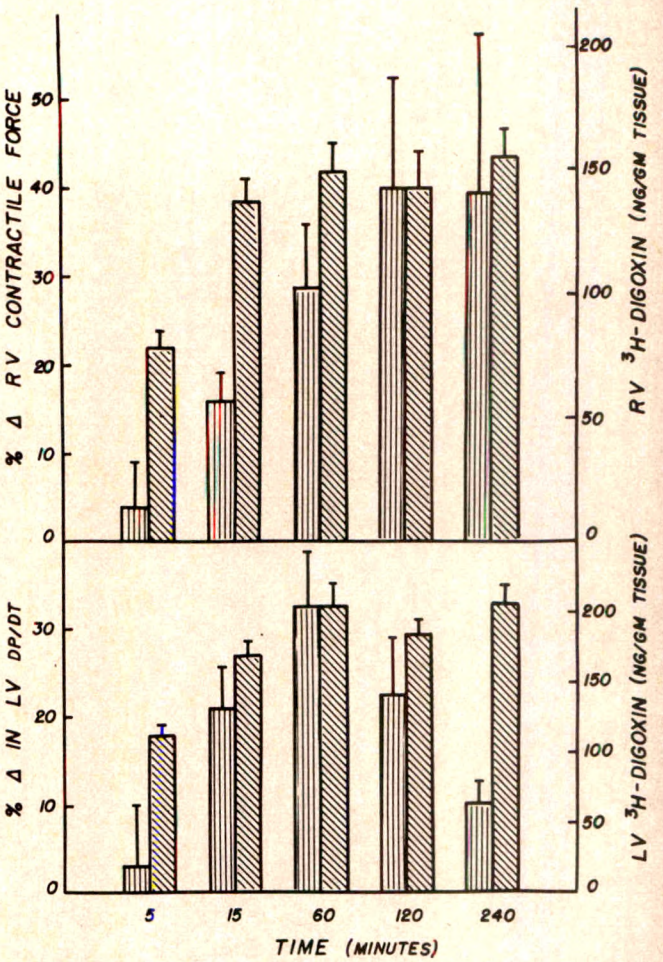

Figure 5. Percentage changes ± SEM of right ventricular contractile force and right ventricle ^{3}H-digoxin concentration (ng/g wet weight ± SEM) in the upper graph, and the percentage changes ± SEM of left ventricular dp/dt and left ventricular ^{3}H-digoxin concentration (ng/g wet weight ± SEM) in the lower section. Vertically striped bars = left ventricular dp/dt and right ventricular contractile force; diagonally striped bars = ^{3}H-digoxin concentration.

receptor site which then secondarily determines the extent of positive inotropy. A number of candidates for this secondary process can be found in previous reports. Govier and Holland[35] demonstrated in isolated rabbit atria that ouabain augmented calcium influx and the exchangeable calcium pool, and that this could increase myocardial contractility. Besch et al.[12] demonstrated that inhibition of sodium, potassium adenosine triphosphatase (Na^+,K^+ ATPase) occurred concomitantly with the development of a positive inotropic effect. The latter investigators suggested that Na^+,K^+ ATPase is the major pharmacologic receptor for cardiac glycosides. Dutta et al.,[36] using an isolated, beating guinea pig heart perfused with ^{3}H-digoxin, showed that the supernatant fraction of the myocardial tissue initially contains the highest concentration of ^{3}H-digoxin but that, by 60 minutes, the greatest concentration is found in the microsomal fraction. These workers suggested

that the microsomal fraction may contain specific receptors for binding digoxin which are necessary for the development of a positive inotropic effect. Their work can be reconciled with that of Besch et al.[12] if the microsomal fraction of Dutta et al.[36] contains Na^+,K^+ ATPase, to which ^{3}H-digoxin binds, thereby inhibiting enzyme activity. Since ^{3}H-digoxin accumulation in the microsomal fraction takes time to occur, this could explain the lag period seen in our study. An alternative explanation, that ^{3}H-digoxin has occupied a specific receptor or entered a specific intracellular compartment but that there is a delay between receptor occupancy and physiologic response, must also be considered, as must the possibility of nonspecific pharmacologically inactive receptor sites.[13] Since, in our present study we measured only total myocardial ^{3}H-digoxin concentration, we are unable to provide data in support of one or another of the postulated mechanisms for the lag period.

Differences in myocardial ^{3}H-digoxin distribution: The distribution of ^{3}H-digoxin in the different chambers of the heart was not uniform. The left ventricle and interventricular septum had a significantly higher ^{3}H-digoxin concentration than either the right ventricle or atria. Other workers[1,37–39] have also noted these differences. The reasons for these differences in ^{3}H-digoxin concentration in the different cardiac chambers are not clear. However, differences in blood flow[40–42] may be an important factor, since right ventricular blood flow has been reported to be approximately 60 to 70 percent and atrial blood flow 45 to 60 percent of blood flow to the left ventricle.[37] Studies to determine the reasons for the differences in myocardial ^{3}H-digoxin distribution are presently being conducted in our laboratory.

In conclusion, the relation of myocardial ^{3}H-digoxin concentration and the hemodynamic effects of digoxin has been described for the first time in the same animals with an intact circulatory system. The time of onset and the peak of hemodynamic effects lagged behind the time of initial uptake and maximal myocardial ^{3}H-digoxin. This suggests that total myocardial ^{3}H-digoxin is not the only determinant of the rate of onset and development of the inotropic effects of digoxin.

Acknowledgments

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Collateral Vessel Development After Right Ventricular Infarction in the Pig

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Although the right coronary artery supplies both ventricles in the pig, a gradual proximal right coronary occlusion produces infarction in the left ventricle, whereas the right ventricle is usually spared. This study evaluates the influence of right ventricular hypertension and hypertrophy (RVHH) on the occurrence of right ventricular infarction and the difference in the rate and extent of collateral vessel development after gradual right coronary occlusion in pigs with (RVHH group) and without (control group) increased right ventricular pressure and mass. Right ventricular hypertension and hypertrophy were induced by pulmonary arterial banding which raised right ventricular systolic pressure from 24 to 74 mm Hg and doubled right ventricular mass in 4 weeks. Right coronary occlusion was produced with an ameroid constrictor in 24 control group pigs and 15 RVHH pigs. Serial selective coronary cineangiograms on days 4, 8, 14, 21 and 28 after ameroid constrictor placement showed no difference in first appearance of collateralization to the occluded right coronary artery. Total collateralization, which was present in all pigs studied in the control group by days 21 and 28, was present in only 57 percent of the RVHH group at the same time. Although left ventricular infarction occurred in all animals in both groups, right ventricular infarction was not found in the control group but was seen in 80 percent of the RVHH group. There was no correlation between the degree of collateralization seen and the size of the right ventricular infarction found. Experimentally induced right ventricular hypertrophy and hypertension make the right ventricle susceptible to infarction and impeded total collateral filling of the occluded right coronary artery in some of the animals studied.

From the Cardiovascular Laboratory, Department of Medicine and Department of Pathology, Duke University Medical Center, Durham, N. C. 27706. This study was supported by U. S. Public Health Service Grants HE 07563, HE 11309 and HE 12506; American Heart Association Grants 66-792 and 69-813; and by grants-in-aid from the North Carolina Heart Association. Manuscript received November 25, 1970, accepted January 27, 1971.

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Right ventricular infarction is rarely seen in man although main stem occlusion of the right coronary artery is common.[1] In man and in the farm pig, virtually all the vascular supply to the right ventricle is from the right coronary artery. In experimental studies in the farm pig we have shown that gradual occlusion of the proximal right coronary artery will produce infarction in the left ventricle while sparing the right ventricle. Furthermore, cineangiographic studies[2] comparing in vivo collateral circulation after either gradual proximal left anterior descending or right coronary arterial occlusion showed that the rate of development of collateral filling of the occluded vessel was more rapid and that complete collateralization occurred faster after right coronary occlusion. This difference in the rate and extent of collateral vessel development was thought possibly to be related to the pressure and mass dissimilarity between the right and left ventricles, and was considered as a possible explanation for the different suscep-

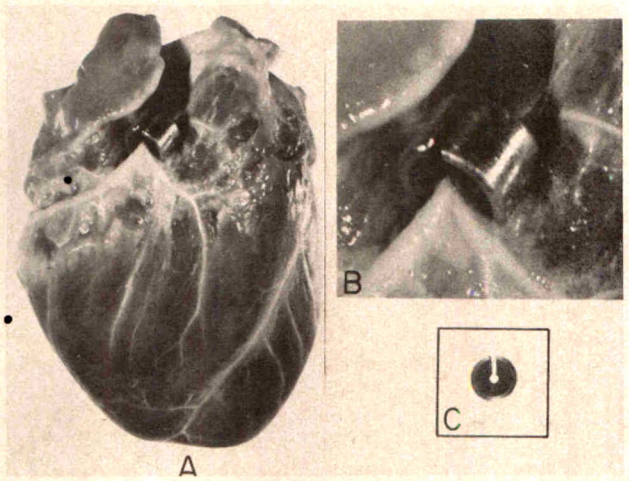

Figure 1. **A,** ameroid constrictor placed on the proximal right coronary artery. **B,** enlarged (×4) section of the ameroid constrictor in place. **C,** end view of the constrictor showing a 1.5 mm central lumen and a 1 mm slit.

tibility of the 2 ventricles to infarction after coronary occlusion. This paper deals with the influence of right ventricular hypertension and hypertrophy on the development of right ventricular infarction after right coronary occlusion in the pig, and examines the effect of increased right ventricular pressure and mass on the time sequence and extent of collateral vessel development after coronary occlusion.

Materials and Methods

Thirty-nine healthy farm pigs were used in the study. Using pentobarbital anesthesia (30 mg/kg), endotrachial intubation, assisted respiration and sterile technique, right ventricular hypertension and hypertrophy were produced in 15 pigs designated as the RVHH group. Through a left thoracotomy, the main pulmonary artery was dissected from the aorta and a double turn of 1 cm wide Dacron® tape loosely placed around the main pulmonary artery. A stainless steel L-shaped rod with a cross-section diameter of 5 mm was placed under the double loop of tape around the pulmonary artery. The tape was then pulled tight and the rod removed from under the tape. The pulmonary arterial lumen, normally 10 mm in diameter, then had the internal diameter opening of the stainless steel cylinder minus the vessel wall thickness or approximately 4 mm. The tape was then sutured in place and the thoracotomy incision closed.

Twenty-eight days after pulmonary arterial banding the 15 pigs of the RVHH group weighing between 28 and 36 lb and 24 pigs of comparable weight who did not undergo pulmonary arterial banding (control group) underwent surgery for placement of a 1.5 mm central lumen diameter ameroid constrictor around the proximal right coronary artery (Fig. 1). Complete occlusion of the vessel usually occurred by 7 days due to the hygroscopic nature of the ameroid. Using this method of producing a gradual proximal coronary occlusion, we have regularly produced left ventricular infarction in the farm pig.[2,3]

Selective coronary cineangiograms by the Sones technique, under light pentobarbital anesthesia and without endotrachial intubation, were performed in pigs in both the control and RVHH groups from 4 to 28 days after placement of the ameroid constrictor. The carotid arteries were exposed under sterile technique and used as the site of entry for a 7.5 Sones catheter. With careful closure of the vessel at the end of the study, many animals could be studied multiple times. There were 41 studies performed on the 24 pigs in the control group and 38 studies on the 15 pigs in the RVHH group (Fig. 2). The cineangiograms obtained using a 5-inch cinefluorographic unit at 60 frames/sec were taken on 35 mm film and reduced on 16 mm film. This permitted good resolution of vessels 300 μ in size. The arteriograms were analyzed for the first appearance of collaterals and for complete collateralization. Collateralization was considered complete when the entire occluded right coronary and its branches were filled by collateral flow.

Detailed gross and histologic examinations of the heart were carried out within 24 hours of death and compared in the 2 groups. Those animals surviving for 28 days after placement of the ameroid constrictor were killed. Multiple sections of the heart, stained with hematoxylin and eosin, Masson and phosphotungstic acid hematoxylin, were examined under the microscope. Infarcts of the interventricular septum were included as left ventricular infarcts. Only those infarcts involv-

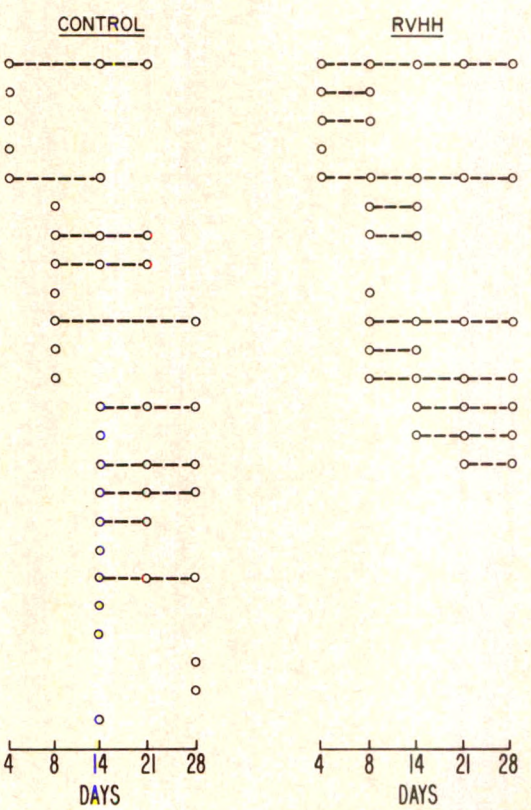

Figure 2. Serial selective coronary cineangiograms were performed in animals in both groups on days 4, 8, 14, 21 and 28 after right coronary occlusion by ameroid constrictor placement. The **dotted lines** connecting the **open circles** represent consecutive studies in the same animal. RVHH = right ventricular hypertension and hypertrophy.

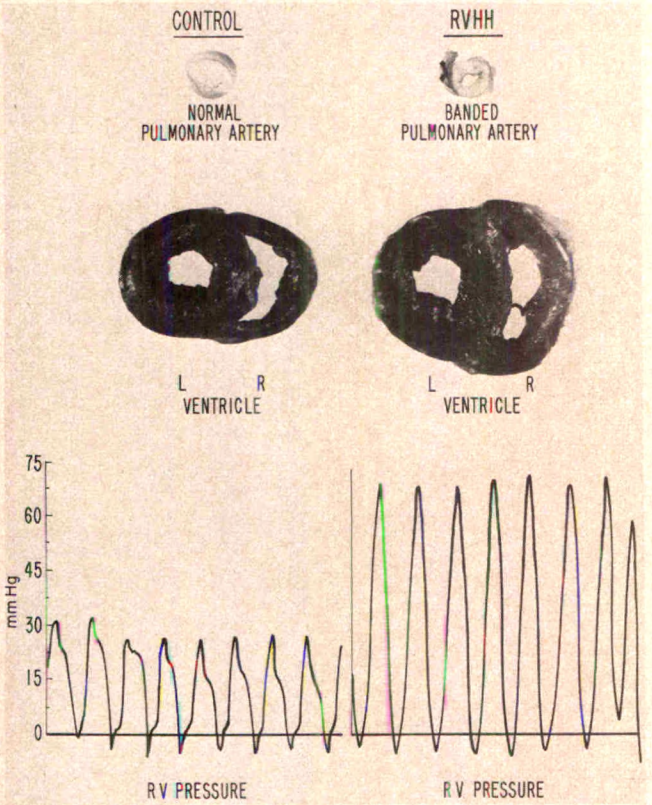

Figure 3. The right ventricular pressure tracing and cross section of the ventricles and pulmonary artery were obtained in animals of both groups with comparable body weight. Sections through the ventricle and pulmonary artery were in the same area so as not to distort comparison of the cross-sectioned size. The diameter of the banded pulmonary arterial lumen is approximately 4 mm.

ing the free wall of the right ventricle were considered right ventricular infarcts.

Results

Production of right ventricular hypertension and hypertrophy: After pulmonary arterial banding, peak right ventricular systolic pressures rose from a normal of 24 ± 4 to 74 ± 6 mm Hg (Fig. 3) and remained at this level over the ensuing weeks. At 4 weeks after pulmonary arterial banding, the right ventricle doubled in relative mass as the percent weight of the right ventricle increased to 64 ± 12 percent from a previously described normal value of 32 ± 4 percent.[4] The percent weight (wt) of the right ventricle was calculated as follows:

$$\%\ \text{wt of right ventricle} = \frac{\text{wt of right ventricular wall} \times 100}{\text{wt of left ventricular wall} + \text{wt of interventricular septum}}$$

Collateral vessel development: The first appearance of collateral filling of the occluded right coronary artery is shown in Figure 4 and is similar in both groups. By day 14 after ameroid constrictor placement all animals had at least some evidence of collateral filling of the occluded right coronary artery. Figure 5 shows a comparison of the number of animals that had complete collateralization as assessed by the day at which complete filling of the occluded right coronary occurred. At days 4 and 8, the percentage of animals studied in each group that had complete collateralization was the same. However, complete collateralization was seen in all animals studied in the control group by day 21 after ameroid constrictor placement and was present in 57 percent of the RVHH group at the same time. Furthermore, at day 28 no further increase in collateralization was noted in those pigs studied in the RVHH group.

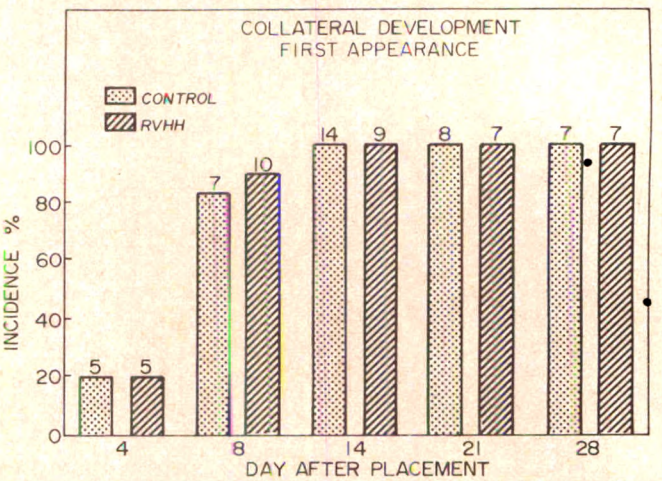

Figure 4. The first appearance of collateral filling of the occluded right coronary artery was noted equally in both groups. The numbers at the top of the bars represent the number of animals studied.

Production of myocardial infarction: Left ventricular infarction was present in all pigs in both the control and RVHH groups. There was no histologic difference in the severity of these infarcts in either group since about 60 percent were transmural. Right ventricular infarction did not occur in the control group, whereas 80 percent of the RVHH group had free right ventricular wall infarcts (Fig. 6). A typical free wall right ventricular infarct is seen in Figure 7. There was no correlation between the degree of right ventricular hypertrophy and hypertension and the size of the right ventricular infarction; and there was no correlation between the degree of collateralization seen and the size of the right ventricular infarct found.

Discussion

It has been observed in man at postmortem examination that right ventricular infarction rarely occurs despite the frequent occurrence of right coronary arterial occlusion.[5,6] However, when

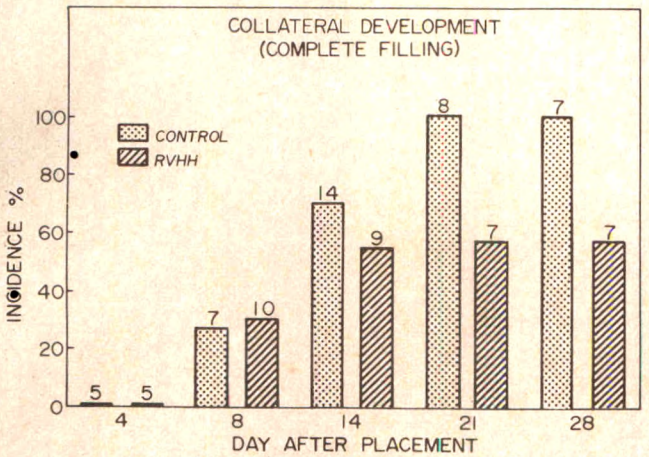

Figure 5. Total collateralization was seen in all animals studied in the control group by days 21 and 28 after ameroid constrictor placement, whereas complete filling of the occluded right coronary artery and its secondary branches occurred in only 43 percent of those in the RVHH group studied at the same time.

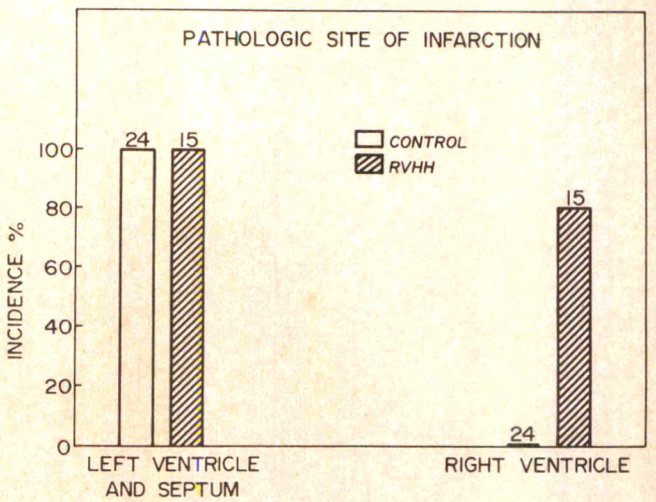

Figure 6. All pigs in the control and RVHH groups had left ventricular infarction. Eighty percent of the RVHH group had right ventricular wall infarction; none in the control group had this finding.

right ventricular infarction is found the presence of pulmonary hypertension and right ventricular hypertrophy is usually noted.[7] Plausible speculation as to why the right ventricle is spared from infarction usually involves the fact that this cardiac chamber is thin-walled and has a low intracavitary pressure when compared to the left ventricle, and may derive significant nourishment from blood coming directly from the cavity.[8] Not only are right ventricular work and oxygen requirement less, but systolic coronary flow is greater in the right coronary artery than in the left coronary system, which may be important during times of ischemic stress.[9] Also, the majority of complete occlusions of the coronary circulation are probably gradual and give sufficient time for intercoronary collateral vessels to form (function) and carry blood from the left coronary system with a high level of intramyocardial resistance to the right coronary system with lower intramyocardial resistance.[10]

In addition, more flow is thought to be readily available from the left coronary system to the right system than vice versa.[11] Our own findings comparing the rapidity and extent of collateral vessel development after right and left anterior descending coronary occlusion in the farm pig seem to bear this out. We found early in vivo development of collateral filling to the occluded right coronary (usually from the left anterior descending artery) as well as more rapid total collateral filling of this vessel.

By creating right ventricular hypertrophy and then gradually occluding the right coronary artery, in essence making the right ventricle similar in mass and wall tension to the left ventricle, we expected to impede both partial and complete collateralization to the occluded vessel, as we had observed after left anterior descending occlusion.[2] However, the first appearance of collateralization was comparable in both the RVHH and control groups. Although the increased incidence of right ventricular infarction in the RVHH group cannot be explained by delayed initial appearance of collateralization, it is not known whether a more rapid or profuse early collateralization in the RVHH group would have spared the right ventricle from infarction. If this latter thought were true, then the degree of early collateralization noted in the RVHH group would have been impeded in relation to the increased wall tension and mass generated by the pulmonary arterial banding.

True impedence of collateralization in some animals can be inferred from examination of those

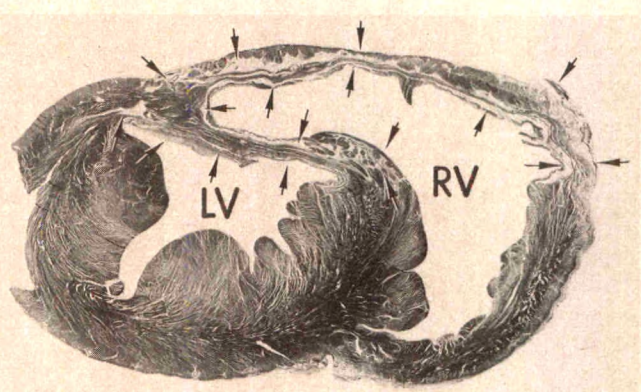

Figure 7. Cross section through the middle third of a heart in a pig with right ventricular hypertension and hypertrophy and an ameroid constrictor placed around the right coronary artery. Healed infarcts (**arrows**) are visible in the posterior left ventricular wall, septum and posterolateral right ventricular wall. Unaffected portions of the right ventricle are hypertrophied. (Masson's trichrome ×2, reduced by 50 percent.)

pigs in the RVHH group examined angiographically at 21 and 28 days after ameroid constrictor placement. Total collateralization occurred in only 57 percent of those examined angiographically. We expected to see large right ventricular infarcts with massive destruction and scarring of the free right ventricular wall in those pigs in which collateralization was incomplete. However, there was no consistent correlation between the degree of collateralization seen and the size of the right ventricular infarct found. What appears to be significant is that within the RVHH group, right ventricular infarction was present despite the relation to the degree of in vivo collateralization and was not seen in the control group. Also, the size of the right ventricular infarction had no relation to the degree of in vivo collateralization visualized during selective coronary cinearteriography.

The conclusions from this study must be that the creation of right ventricular hypertension and hypertrophy plays an etiologic role in producing right ventricular infarction after a gradual right coronary occlusion in the farm pig. The production of right ventricular hypertension and hypertrophy does not necessarily slow the rate and extent of collateral vessel development after gradual right coronary occlusion; however, in some animals examined total collateralization was prevented, but this had no bearing on the size of the infarction found at postmortem examination.

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Peritoneal Dialysis for Intractable Heart Failure in Acute Myocardial Infarction

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Brooklyn, New York

This report deals with 4 patients with intractable heart failure following an acute myocardial infarction who evidenced significant immediate benefit from peritoneal dialysis. In 3 patients, loss of edema fluid, abolition of life-threatening arrhythmias, restoration of normal mentation and electrolyte normality, reduction of blood urea nitrogen and return of urinary output were achieved. Before dialysis, increasing doses of digitalis and potent diuretic agents failed to relieve pulmonary edema or reduce venous pressure and oliguria increased.

Peritoneal dialysis can be safely and effectively employed during the course of an acute myocardial infarction for intractable congestive heart failure.

Peritoneal dialysis has become an acceptable therapeutic approach for the treatment of renal failure of various causes, owing to improved equipment and available fluids.[1,2] In addition, peritoneal dialysis has been successfully employed for the treatment of refractory congestive heart failure.[3–5] However, renal function may be drastically and suddenly reduced after acute myocardial infarction as a result of diminished renal blood flow that accompanies the decreased cardiac output. Peritoneal dialysis may be required in such cases despite the availability of potent diuretic agents[6,7] for treating heart failure and edema in patients with myocardial infarction.

Patients

This report concerns 4 patients with an acute myocardial infarction who were admitted to the coronary care unit of the Brooklyn Hospital during a 4 year period. Each patient had progressive intractable congestive heart failure with pulmonary edema, ascites, leg edema, orthopnea, venous distention, increasing blood urea nitrogen, decreasing serum sodium, aberrant mentation and various cardiac arrhythmias. No response was achieved with digitalis and increasing doses of diuretic agents. Peritoneal dialysis was then performed by standard techniques with rapid relief of pulmonary edema and fluid overload, and correction of blood electrolyte levels in all patients. The procedure was uncomplicated and tolerated well.

All 4 patients had a history of coronary artery disease and congestive heart failure before the current acute myocardial infarction. Three of the 4 had known diabetes mellitus, 2 had known renal disease and 1 had probable renal disease before admission.

All 4 patients had an acute anterior wall myocardial infarction and had had 1 episode of ventricular tachycardia during the immediate acute course. Two patients had ventricular fibrillation, and 3 needed precordial direct-current shock therapy. Two patients required thoracentesis. All patients had received digitalis, furosemide and lidocaine. Table I shows the laboratory values before and after dialysis, and Table II indicates the volume of fluid removed by dialysis in each patient. Three pa-

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TABLE I

Blood Chemistry Values Before and After Dialysis*

	Case 1		Case 2		Case 3		Case 4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Sodium	119	136	120	141	110	131	131	142
Potassium	2.8	4.5	2.5	4.5	4.2	3.7	7.1	4.0
Chloride	90	101	81	108	85	96	83	93
CO_2	10.3	21	33	22	18.5	25	22	23
Blood urea nitrogen	87	49	62	25	51	26	48	29
Creatinine	7.2	5	2.1	2.0	3.3	1.4	...	...
Central venous pressure	20	12	...	...	21	5	19	10

Pre = before dialysis; post = after dialysis.

* Sodium, potassium, chloride, CO_2 values in milliequivalents per 100 ml; blood urea nitrogen and creatinine values in milligrams per 100 ml; CVP values in millimeters of water.

TABLE II

Number of Exchanges and Volume of Fluid Removed

	Case 1	Case 2	Case 3	Case 4
Exchanges	65	20	24	10
Negative balance in ml	8,675	4,450	8,300	3,100

tients responded well to oral diuretic agents and digoxin after the completion of peritoneal dialysis. Cardiac arrhythmias ceased in 3 patients after peritoneal dialysis.

Case Reports

Case 1: A 74 year old man with a 6 month history of coronary disease, arrhythmias and congestive heart failure was admitted with an acute anterior myocardial infarction, supraventricular tachycardia, congestive heart failure and elevated serum enzyme levels. Digoxin, ethacrynic acid, furosemide, diphenylhydantoin, procainamide and lidocaine were administered as indicated. Fifty watt seconds of direct-current precordial electroshock were required for ventricular fibrillation. The patient had 1 episode of cardiogenic shock with a blood pressure of 70/40 mm Hg which responded to norepinephrine, dextran and metaraminol.

On day 3 pulmonary edema developed with a central venous pressure of 20 mm H_2O, blood urea nitrogen of 87 mg, 100 ml potassium of 2.8 mEq, and a 6 hour urinary output of 45 ml. Peritoneal dialysis was performed with 65 exchanges and a total negative balance of 8,675 cc. The patient's condition improved clinically; he became mentally clear, and the pulmonary edema disappeared; the central venous pressure dropped to 12 mm H_2O with correction of blood electrolyte and urea nitrogen values. His condition subsequently improved, and he was discharged from the hospital 1 month later without congestive heart failure, with sinus rhythm, and a blood pressure of 110/60 mm Hg. He died 13 months later of bronchopneumonia and gram-negative bacterial sepsis.

Case 2: A 58 year old housewife was admitted with an extensive anterior myocardial infarction. She had an 18 year history of diabetes mellitus, hypertension and coronary disease with a previous infarction and compensated congestive heart failure. Progressive congestive heart failure developed, which failed to respond to increasing doses of digitalis and furosemide. Falling blood electrolyte values and decreased urinary output were accompanied by increased blood urea nitrogen. Tachyarrhythmias, including ventricular tachycardia requiring lidocaine, recurred, and gallop rhythm as well as pleural effusion requiring thoracentesis developed.

On day 10 peritoneal dialysis was instituted with 20 exchanges and a negative balance of 4,450 ml. The patient's condition showed immediate remarkable improvement with loss of pulmonary edema and cyanosis. Respiratory and cardiac rates diminished, and ventricular arrhythmias ceased. Serum electrolyte values improved toward normal, and the patient was discharged home 3 weeks later, fully ambulatory.

Case 3: A 64 year old man with known diabetes, a previous myocardial infarction and heart failure was admitted with acute myocardial infarction and exacerbation of heart failure. He had been receiving digoxin, chlorothalidone, spironolactone, furosemide and intermittent mercurial diuretic agents. He had changing cardiac rhythm including atrial fibrillation, atrial flutter, ventricular tachycardia and a cardiac arrest. He was treated with intravenously administered lidocaine and precordial direct-current shock, and he required resuscitation with external massage for a cardiac arrest. He had intractable heart failure, pulmonary edema, stupor, unresponsiveness to diuretics and digitalis, as well as severe electrolyte imbalance.

Peritoneal dialysis was instituted on day 5 and after 24 exchanges there was a resultant negative balance of 8,300 ml. He had dramatic improvement with return of mentation, loss of cyanosis and pulmonary edema, and marked improvement in electrolyte values. Cardiac rhythm stabilized. He was discharged home ambulatory after 3 weeks and continued to have compensated heart failure.

Case 4: A 62 year old woman with diabetes and angina pectoris was admitted with an extensive anterior wall myocardial infarction. Congestive heart failure developed which required digitalization; thoracentesis for a right pleural effusion was performed on days 4 and 18. A pericardial friction rub was present. On day 18 ventricular fibrillation developed requiring direct-current shock for cardioversion to sinus rhythm on 2 occasions. She was given lidocaine intravenously for ventricular instability. Heart failure was progressive with elevation of central venous pressure to 19 mm H_2O and heart rate to 120 beats/min. Pulmonary edema was present, and the serum potassium level rose to 7.1 mEq. Peritoneal dialysis was instituted on day 18 when anuria was noted. After 10 exchanges a negative balance of 3,100 cc was achieved. Pulmonary congestion cleared and the serum potassium level fell to 4.0 mEq. Twelve hours later she had a cerebrovascular accident with coma, followed by cardiac arrest which was not treatable, and she died.

Discussion

The need for an alternative method of treating intractable congestive heart failure when diuretic agents and digitalis have failed has been met by peritoneal dialysis.[3-5] The occurrence of progressive electrolyte derangement and uremia diminishes the continued effectiveness of diuretic agents. In acute myocardial infarction, the sudden drop in cardiac output and renal blood flow may precipitate or aggravate congestive heart failure and require the immediate relief of hypervolemia and pulmonary edema by peritoneal dialysis. Fatal and life-threatening cardiac arrhythmias due to electrolyte abnormality may be abolished by the rapid institution of peritoneal dialysis. Cardiac recuperation, otherwise hopeless, may then be achieved. Chopra et al.[8] have reported the successful application of peritoneal dialysis for pulmonary edema in 3 of 4 patients with acute myocardial infarction.

This report demonstrates the successful employment of peritoneal dialysis when all other means of reversing congestive heart failure had failed. The 2 men survived 13 months each. One died with bilateral bronchopneumonia and gram-negative bacterial sepsis, and the other still survives. One of the 2 women survived 3 weeks, only to be rehospitalized and die from cardiac arrest. The other patient had a cerebrovascular accident and died 24 hours later. All of these critically ill patients showed definite unequivocal lessening of heart failure, and 3 of the 4 patients achieved relative normalcy after peritoneal dialysis.

The patients in this series were afflicted with chronic coronary artery disease and preexisting compensated heart failure prior to the acute infarction. It is of interest to note that all the infarctions were anterior and extensive by electrocardiographic criteria. The arrhythmias reflected the irritable state of the myocardium in these patients. None of the patients were thought to have digitalis toxicity. Diabetes mellitus and renal disease were present in 3 of the 4 patients. Such complications underscore the severe arterial disease in these patients and gravely worsen the prognosis for intractable heart failure without peritoneal dialysis. The high late mortality rate in these patients reflects the presence of advanced occlusive vascular disease.

Peritoneal dialysis has been used to reverse severe congestive heart failure before cardiac surgery.[9] Raja et al.[10] have reported 8 repeated peritoneal dialyses in a 21 month period in 1 patient with congestive heart failure with excellent results.

Large intravenous doses of furosemide in the presence of uremia, hyponatremia and hypochloremia will produce diuresis in some patients, obviating the indication for peritoneal dialysis.[11] The fact that only 4 patients in 850 admissions in 4 years of operation of our coronary care unit required peritoneal dialysis is adequate evidence that other measures are usually successful in treating severe congestive heart failure associated with acute myocardial infarction. Indeed, it is our belief that the early judicious use of digitalis at the first sign of congestive heart failure has materially reduced the incidence of severe congestive heart failure and shock accompanying acute myocardial infarction. Conceivably, the incidence of acute renal tubular necrosis is also lessened. The coronary care unit has reduced the hospital mortality rate of acute myocardial infarction by at least 10 percent by preventing and treating life-threatening arrhythmias.[12] Heart failure and shock remain the most common causes of death from acute myocardial infarction.[12]

Peritoneal dialysis can be used as a rapidly effective temporary measure when other therapy fails. Although peritoneal dialysis can be safely performed during the course of an acute myocardial infarction, it is not to be considered routine therapy for congestive heart failure in such circumstances.

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The Effect of Age on the Electrocardiogram

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There are significant electrocardiographic age trends in adult healthy populations from the third to the fifth decade in QRS and T amplitudes (decrease with age) and direction (left axis shift with age) in conventional electrocardiographic leads, which flatten out after age 50. The decrease of amplitudes is more pronounced in men than in women. Age trends of intervals are absent or small. However, the incidence of premature supraventricular and ventricular beats increases with age. Overweight accelerates the age trends. Diagnostic implications are discussed, particularly for recognition of left ventricular hypertrophy. Magnitudes and directions of maximal spatial QRS and T vectors show age trends similar to comparable conventional electrocardiographic items. Initial spatial 20 msec vectors also decrease with age; therefore, "poor progression of the R wave in the anterior chest leads," often interpreted as compatible with anterior wall myocardial infarction, is a normal age trend. In the majority of studies, the effect of age is more pronounced in populations with high prevalence of coronary artery disease than in populations with low incidence. Coronary artery disease, as long as the resting electrocardiogram is normal, accelerates the age trends. The frequency of ischemic response to exercise is greater, with more pronounced age trends, in populations with high prevalance of coronary artery disease. It is concluded that the electrocardiographic age trends in asymptomatic populations are to a large extent due to latent coronary artery disease.

General Methodology

Information about the effect of age on the electrocardiogram is important for accurate recognition of abnormalities in older persons, and for exploration of the relation between the electrocardiographic age trends and prevalence of latent coronary insufficiency.

The ideal method for investigation of age trends is longitudinal research. Because of the long time needed for follow up, few such studies with detailed measurements of electrocardiographic items have been undertaken. The most important longitudinal study is that of 1,000 healthy aviation personnel who were first investigated at the mean age of 24 years[1] and later at the mean ages of 36, 42 and 48 years[2]; 719 healthy men were followed up through ages 42 to 48 years. In a significant number heart disease or abnormal electrocardiographic findings developed.

The bulk of information on age trends has been obtained in cross-sectional studies with the conventional electrocardiogram. Additional recent information from the vectorcardiogram and particularly the exercise electrocardiogram has become pertinent.

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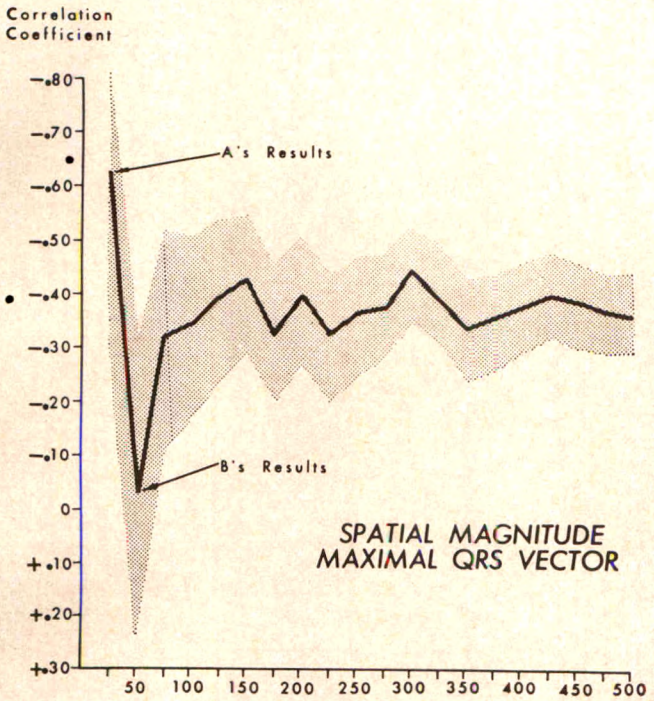

Figure 1. The **heavy line** indicates correlation coefficients (r) between age and spatial maximal QRS vector for various sample sizes, shown on the **abscissa.** The **shaded area** represents the extent of the confidence limits of r. (Reprinted from Pipberger[3] by permission of the American Heart Association, Inc.)

The analysis of electrocardiographic age trends is complicated because of interaction with other constitutional factors, such as body weight, sex, race, chest configuration and functional variables such as blood pressure. The sample must be large enough either to cancel out or preferably to analyze separately other variables affecting the electrocardiogram. The necessity of large sample size has been demonstrated by Pipberger et al.[3] Figure 1 shows the variation of the correlation coefficient (r) between age and the spatial maximal QRS vector, with confidence limits, dependent on the sample size. Small sample sizes, that is, up to 200, show huge variations, and the correlation coefficient stabilizes only over 500. It is not surprising that with groups of less than 200, as were used in gerontologic research, conflicting results have been obtained.

Another prerequisite for the validity and clinical utilization of the data is that the sample should be representative of average, healthy persons, carefully screened with independent methods for absence of recognizable disease. The sample of Pipberger et al.[4] of 518 hospitalized patients with a normal cardiovascular system is not fully representative of a healthy, average population. On the other extreme, the sample of over 6,000 U.S. Air Force flying personnel investigated by Hiss et al.[5] is highly preselected as to physical fitness. These 2 large samples include only men.

In this review, the discussion of age trends in the conventional electrocardiogram will be based mainly on our own material of 960 healthy men and women.[6] It has been supplemented by data from extensive epidemiologic studies[7,8] in different European and Asiatic countries.

General Age Trends—Conventional Electrocardiogram

Within this presentation, we will be concerned with age trends among adults only.

Age trends in the conventional electrocardiogram can be briefly summarized: The amplitudes of all deflections decrease together with directional (axis) changes (left axis shift in frontal plane; clockwise rotation in horizontal plane). Age changes of the intervals are less pronounced or absent. The R–R interval (heart rate) and the QRS interval show no significant age trends. A slight but significant increase of the P–R interval of about 0.01 second[3,7,9] occurs from the third to sixth decades. Therefore, a value of 0.22 second is proposed for the upper normal limit for persons over 50 years of age. The frequently used limit of 0.20 second is too conservative. The Q–T interval, corrected for heart rate,* increases significantly by about 0.01 from the third to sixth decades.[10] Pipberger et al.[4] reported a very slight but significant increment of P wave duration of 0.008 second from the third to the seventh decades.

Table I shows some diagnostic consequences resulting from disregard of age trends for 4 electrocardiographic items. ΣQRS is the algebraic sum of the largest positive and negative QRS deflections of the standard leads, which is reasonably representative for overall frontal plane QRS amplitude. The percentage exceeding these normal limits obtained in older men is several times greater than that in younger men, resulting in an appreciable number of false diagnoses of abnormality.

* Using a regression equation obtained with aid of an electronic computer, which gives a better fit than Bazett's[11] widely used square root equation[11] (Simonson et al.[10]).

TABLE I

Percentage of Normal Men Exceeding Accepted Normal Limits of Electrocardiogram

Item	Limit	Younger Men (%)	Older Men (%)
P–R	0.21 sec	0.6	3.4
ΣQRS	15.0 mm	6.4	11.2
Q_3	25% of maximal R	3.2	9.0
$S\text{–}T_{1,2}$	−0.5 mm	2.5	7.3

ΣQRS = algebraic sum of positive and negative QRS deflections in leads I, II and III. (Reprinted from Simonson.[6])

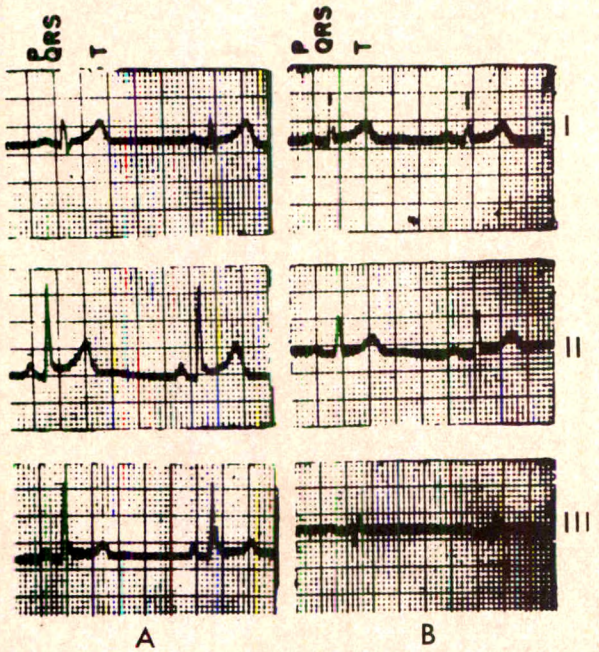

Figure 2. Electrocardiograms of a healthy young man 22 years of age (A) and a healthy older man 51 years of age (B) representative of their age groups. In the older man, the QRS and T amplitudes are smaller, the QRS and T axes are shifted to the left, and the P–R interval is longer. (Reprinted from Simonson.[9])

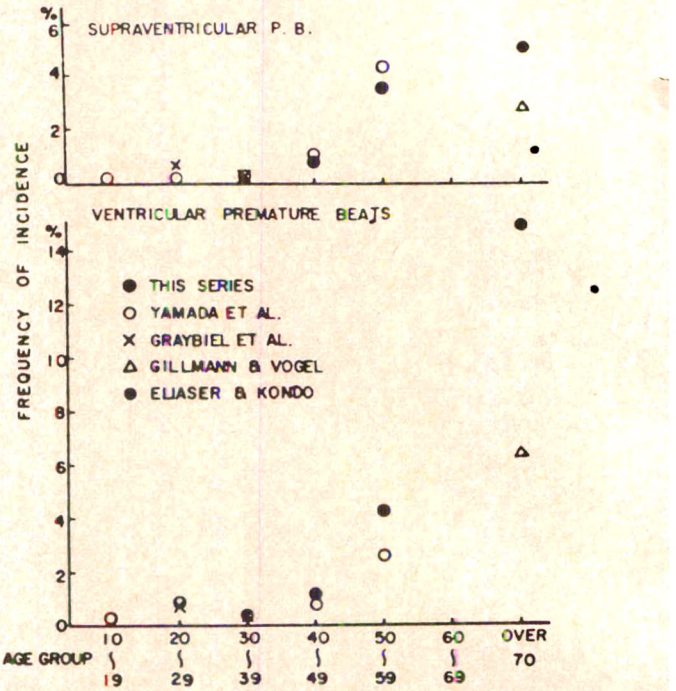

Figure 3. The age trend in the frequency of ventricular and supraventricular premature beats in healthy subjects, as reported by several authors. (Reprinted by permission from Okajima et al.[16])

Figure 2 shows the standard electrocardiographic leads in a healthy man of 22 years (A) and a healthy older man of 51 years (B), fairly representative for their age groups. We tried to select subjects with electrocardiograms close to the group means for the P–R interval, QRS amplitude and axis and T wave amplitude and axis.[9] To find suitable tracings for this demonstration, over 500 electrocardiograms were scanned, which is in line with statistical expectation.[12] Although both electrocardiograms of Figure 2 would be interpreted as normal, they are quite different (longer P–R interval, smaller amplitude and left axis deviation of QRS complex and T wave in the older subject).

TABLE II

Comparison of Decrease in Electrocardiographic Amplitudes (in millimeters = 0.1 mv) with Age in Men and Women

	Men			Women		
	M_1 (no. = 115)	M_2 (no. = 424)	M_2 (100)/ M_1	M_1 (no. = 104)	M_2 (no. = 142)	M_2 (100)/ M_1
R_2	11.7	7.5	64	9.9	8.1	82
T_2	2.9	2.3	80	2.4	2.2	93
ΣQRS	28.2	19.8	70	22.6	20.3	90
ΣT	6.1	5.0	82	5.3	4.9	93
$R–V_4$	16.6	14.2	86	11.5	12.4	108
$S–V_2$	18.0	12.7	71	12.4	9.4	76
$T–V_2$	6.5	5.5	84	3.1	3.0	94

M_1 = means for group 20 to 29 years of age; M_2 = means for group 40 to 59 years of age; $M_2(100)/M_1$ = relative decrease in percent; ΣQRS = algebraic sum of positive and negative QRS deflections in leads I, II and III; ΣT = algebraic sum of T waves in leads I, II and III. (Condensed from Simonson.[6])

Of considerable clinical interest is the incidence of premature beats in clinically healthy subjects as shown in Figure 3, compiled from different samples[2,13–15] by Okajima et al.[16] of American, German and Japanese populations. In all samples, the frequency of premature beats (in percent of regular beats) particularly ventricular beats increases over age 40 years. As upper normal limit a frequency of 5 percent may be proposed for supraventricular beats and for ventricular beats up to age 60 years, and 10 percent for premature ventricular beats in persons over 60 years.

Interaction of Age Trends with Other Constitutional Variables

We will limit the discussion to interaction of electrocardiographic age trends with sex and weight and to comparison of age trends in different populations. The effect of blood pressure up to a systolic pressure of 180 and a diastolic pressure of 100 mm Hg has been slight or absent.[6,17] Rautaharju and Blackburn[18] found the age trend of the QRS axis to be independent of blood pressure.

Effect of Sex on Electrocardiographic Age Trends

The electrocardiographic age trends are significantly steeper in men than in women. Table II

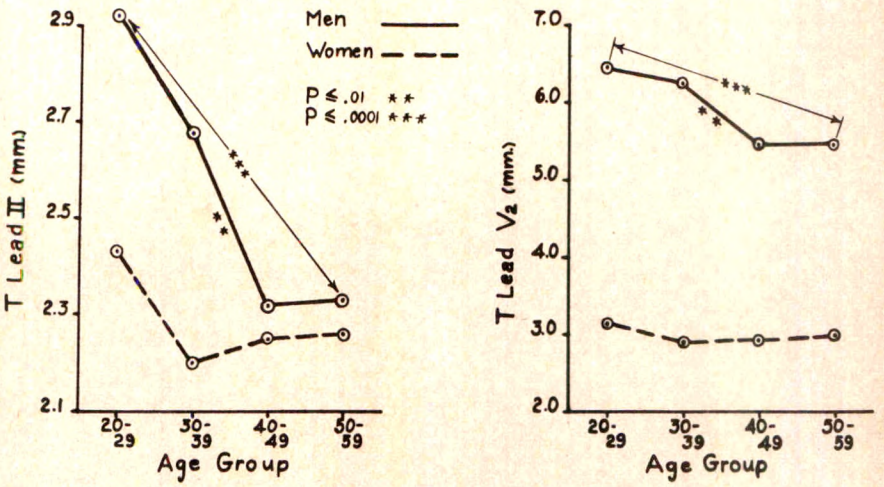

Figure 4. Changes of T wave in leads II (**left**) and V_2 (**right**) in men and women from 20 to 60 years.

shows the age differences between young (20 to 29 years) and older (40 to 59 years) men and women in 7 selected representative electrocardiographic amplitude items. Since the age trends flatten out after age 40 years (confirmed by Blackburn et al.[17]), the age groups 40 to 49 and 50 to 59 are combined. The relative change in percent of the value at ages 20 to 29 is greater in men than in women, particularly for the R wave in lead II, ΣQRS and the R wave in V_4. The amplitudes are smaller for women, more so at ages 20 to 29, so that the age difference decreases with age. In a substantial number of electrocardiographic items, the age trends in women are not statistically significant. Figure 4 shows, as an example, the age changes of the T wave in lead II (left) and in lead V_2 (right). On the other hand, there is no significant sex difference in the left QRS axis shift from 62.6° in men and 61.6° in women at ages 20 to 29, to 36.2° (men) and 36.1° (women) at ages 50 to 59. In both men and women, the QRS axis shift with age is pronounced (Fig. 5). It is of importance for clinical application that this shift has a greater effect on the lower than on the upper normal limits (97.5 percentile) due to a different skewness of frequency distribution in the different age groups. In men, the upper normal limit at ages 20 to 29 is 95.9°; at ages 40 to 59 it is 87.9°, a difference of 8°. The low normal limits change from 2.9° to −28.4°, a difference of 30.9°. A QRS axis of −10° would be within normal limits for a person over 30 years of age, but would be abnormal for a patient under 30 years. Thus, the age trends interfere to a greater extent with the recognition of left than right ventricular hypertrophy. The QRS axis shift in the horizontal plane (shift of the transitional zone in clockwise rotation) is significant in men, but does not reach statistical significance in women.

The findings of Hiss et al.[5] of decreased QRS and T amplitudes in men agree well with our results. Table III shows the changes of 4 selected

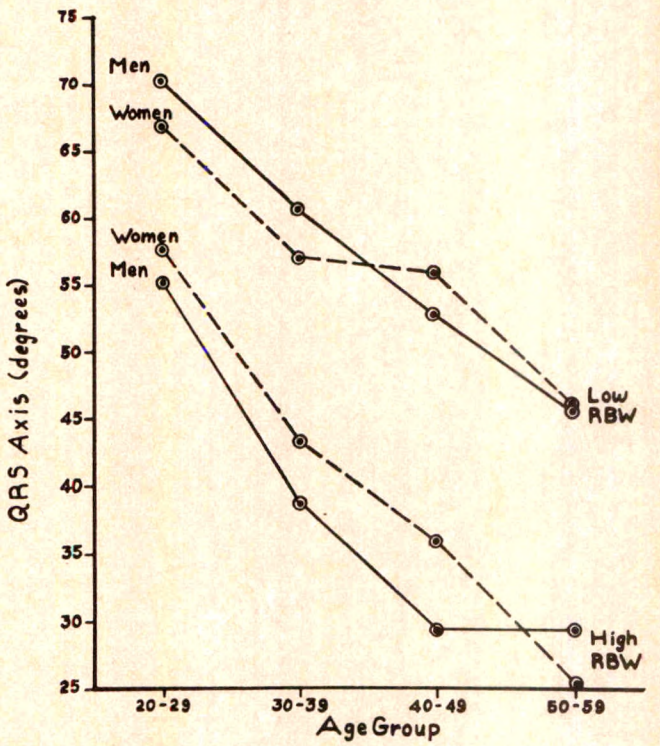

Figure 5. QRS axis shift with age in men and women with low and high relative body weight (RBW). In overweight men and women, the QRS axis is shifted to the left, and the age trend is somewhat steeper. (Reprinted by permission from Simonson.[6])

TABLE III

Age Trends of Selected Electrocardiographic Items (Means) in a Longitudinal Study of 1,000 Aviators

Age	R_2 (mm)	T_2 (mm)	ΣQRS (mm)	ΣT (mm)
24	11.4	3.4	28.2	6.76
36	9.2	2.4	23.5	4.88
42	8.2	2.5	23.1	4.63
48	...	...	20.1	5.16

(Condensed with permission from Harlan et al.[2])

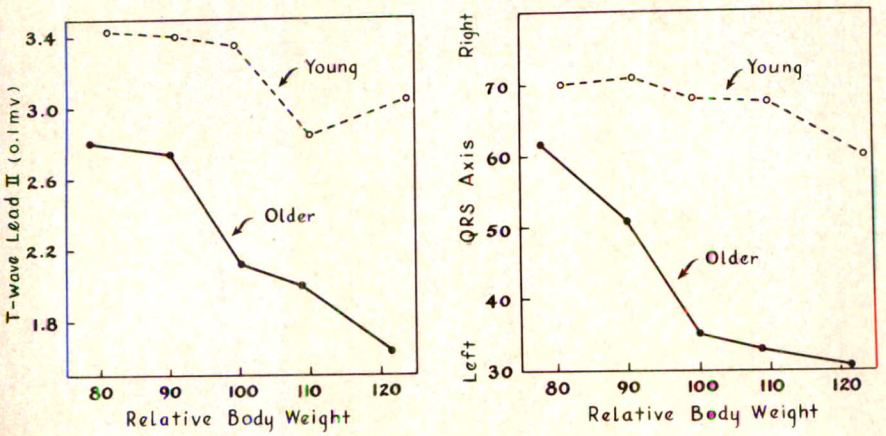

Figure 6. Effect of relative body weight (RBW) on amplitude of the T wave in lead II (left) and QRS axis (right) in young and older men. The effect is more pronounced in older men.

electrocardiographic items in the longitudinal study of Harlan et al.[2] on originally 1,000 healthy men. The age trends in the cross-sectional study (Simonson,[6] Table 2, Fig. 5) as well as the normal (97.5 and 2.5 percentile) limits for the different age groups are very similar. "Comparable values from our longitudinal evaluation are strikingly similar, suggesting the validity of his [Simonson] cross-sectional surveys and the electrocardiographic similarity of these two groups of healthy men" (Harlan et al.[2]). The good agreement shows that both groups are representative of a healthy American male population.

Age and Relative Body Weight

The relative body weight, in percent of a "normal" body weight derived from the height-weight ratio of the Medico-Actuarial mortality investigation tables,[19] was used as an index for a gross estimate of underweight, normal weight and overweight. Since the relative body weight in these tables was corrected for age, it does not reflect the increase of absolute body weight with age, which is due to increased fat content, determined by densimetry.[20] Therefore, at the same relative body weight, an older man is more obese than a younger man. Our sample was subdivided into 5 relative weight groups from 80 percent (underweight) to 120 percent (overweight); 100 percent represents normal relative body weight. The effects of relative body weight and age are synergistic, with a tendency to smaller QRS and T amplitudes and left QRS axis shift. The changes of amplitudes with relative body weight are more pronounced in older than in younger subjects. This is illustrated in Figure 6 for the T wave in lead II (left) and QRS axis (right) from a sample of 157 young men (18 to 28 years) and 233 older men (50 to 60 years).[21] The range of mean relative body weight from 78 percent (pronounced underweight) to 122 percent (pronounced overweight) is quite large. Therefore, the weight difference of electrocardiographic items increases with age.

The more pronounced effect of relative body weight on electrocardiographic amplitudes in older men was confirmed in the larger sample of 960 men and women[6] and may be due to the greater fat content. The left axis shift of the QRS axis in men and women is steeper with high relative body weight than with low relative body weight (Fig. 5). In all age groups, the QRS axis is oriented more to the left in groups with greater relative body weight. As a general conclusion, overweight tends to accelerate the age trends. Clinically, relative body weight should be considered together with age in the differentiation between normal and abnormal, more so in older patients.

Age Changes in the Vectorcardiogram

In a comparison of mean spatial QRS and T vectors, constructed from the conventional electrocardiographic leads, significant differences between 105 young (18 to 28 years) and 178 older (50 to 59 years) men were noted.[22] The magnitude of both vectors was significantly smaller in older men, and they were oriented more superiorly (elevation).

In the follow-up series of Harlan et al.,[2] the left axis shift of mean and "initial" (0.04 second)* QRS frontal plane vectors and mean T vectors, constructed from conventional leads, in the interval of 18 years was the more pronounced the greater the weight gain; this finding is in excellent agreement with data from the cross-sectional studies.

The conventional electrocardiographic leads have a considerable electrical distortion; therefore, the study by Pipberger et al.[4] with the Frank lead system gives more accurate information. Figure 7 shows the relative (value at ages 20 to 29 taken as 100) decrease of the spatial QRS and ST–T vectors, as sum of all instantaneous vectors, with age. In contrast to the electrocardiographic

* The mean 0.04 second vector is not truly an initial vector, as often referred to. The 0.04 second vector, in Grant and Estes' definition,[23] used by Harlan et al.,[24] is the mean integral vector from zero to 0.04 second; 0.04 is usually the mid-point of the QRS interval.

age trends of ΣQRS and ΣT, which flatten out after age 40 years, the drop continues to ages 60 to 78 years, and is steeper for the ST–T vector than for the QRS vector. This may be due to the fact that the electrocardiographic scalar ΣQRS and ΣT and the sum of instantaneous spatial QRS and T vectors, although related, are not identical or to the different sample composition as discussed earlier. Up to ages 40 to 59, the relative decrease of QRS and T vectors in Figure 7 is quite similar to that of QRS and T amplitudes of the conventional electrocardiogram shown in Table II.

Table IV shows a condensation of age trends in some other vectorcardiographic items in the investigation of Pipberger et al.[4] In the frontal plane loop, the maximal QRS vector is more superiorly oriented (corresponding to left axis deviation), and in the horizontal planar projection, more leftward. Of particular interest is the decrease of the initial 20 msec vector (in lead Z and spatial). With relation to the conventional electrocardiogram this corresponds to the so-called poor progression of the R wave in the anterior conventional chest leads V_1 to V_3, which is a normal age trend. Consequently, recognition of anterior wall myocardial infarction is more difficult in subjects over age 50 years.

Cause of Electrocardiographic Age Trends

None of the physiologic aging processes found in other tissues, organs and functions have been identified with electrocardiographic age trends, but their involvement cannot be ruled out. Whether the loss of active tissue, as a general feature of aging, applies to the heart is questionable. The heart weight does not show any decrease with age in autopsy material of patients with a normal cardiovascular system.[24] However, this does not rule out possible replacement of some myocardial fibers by fibrosis. It may be suspected that the left QRS axis shift with age may be due to a relative left ventricular hypertrophy, but in the absence of heart disease or arterial hypertension there is no age trend of the left/right ventricular ratio.[24]

Asymptomatic coronary atherosclerosis: The discussion, therefore, has been centered on possible involvement of latent asymptomatic coronary artery disease as a cause for the electrocardiographic age trends. Atherosclerotic degeneration of coronary arteries is common in older Americans who die of noncardiac causes according to Clawson's large material[25,26] of 30,265 autopsies. In the autopsy data of White et al.[27] of 600 male hearts, there was a continuous trend of increasing coronary sclerosis from ages 35 to 55 years, but no further increase beyond age 55; this finding agrees fairly well with the electrocardiographic age trends in our material and that of Blackburn et al.[17] One of the most detailed studies with microscopic measurements in 536 hearts of normal patients is that of Lober.[28] The intima of coronary arteries thickens and the lumen narrows progressively with age, quite parallel to electrocardiographic age trends. Coronary atherosclerosis is obviously widespread in the population of the United States, and only a minority experience overt clinical coronary insufficiency.

There is a progressive increase of some electrocardiographic abnormalities with age in an

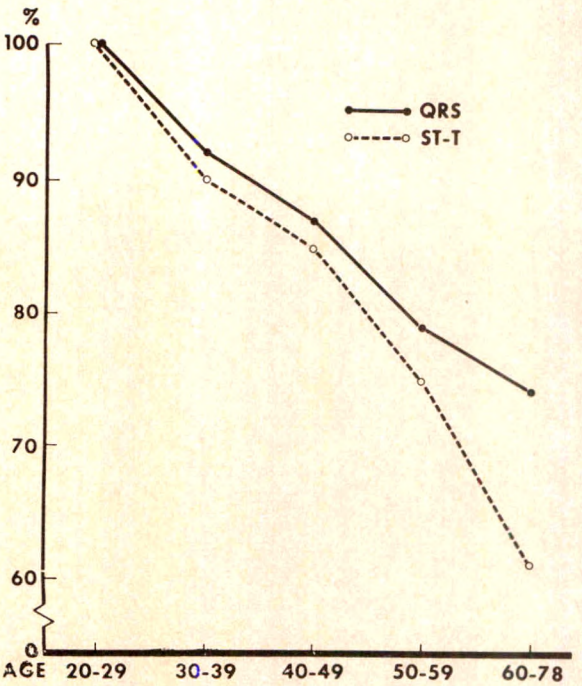

Figure 7. Decrease of spatial magnitudes of QRS and ST–T complexes with age. To obtain representative voltage values for the entire complex, amplitudes of all instantaneous vectors were combined. The results in the youngest age group were taken as 100 percent. The percentage decreases of all vectors of each consecutive group were then averaged and plotted on the ordinate. The age is indicated on the abscissa. (Reprinted from Pipberger[4] by permission of the American Heart Association, Inc.)

TABLE IV

Vectorcardiographic Age Trends in 518 Men Free of Cardiovascular Disease

Item	Age Groups (yr) 20–29 (no. = 78)	30–39 (no. = 179)	40–49 (no. = 151)	50–59 (no. = 56)	69–78 (no. = 54)	P Value 20–29 vs. 69–78 Years
0.02 sec Z (mv)	0.30	0.26	0.24	0.18	0.17	<0.001
0.02 sec spatial (mv)	0.36	0.31	0.27	0.24	0.22	<0.001
Max direction (°FP)	50	41	42	38	32	<0.001
Max direction (°HP)	312	325	326	331	340	<0.001
Max T spatial (mv)	0.50	0.45	0.42	0.40	0.31	<0.001

FP = frontal plane; HP = horizontal plane.
(Condensed from Pipberger et al.[4])

TABLE V

Mean Age Differences in Several Electrocardiographic Items in American and Japanese Men

Item	American Men		Japanese Men	
	20–29 Years	40–59 Years	20–29 Years	40–59 Years
R wave, lead V_5 (mm)	15.3	14.1	16.6	17.5
S wave, lead V_1 (mm)	11.4	8.6	9.4	8.9
T wave, lead II (mm)	2.9	2.3	3.5	3.5
QRS axis (°)	63	37	64	54

(Condensed from Simonson.[12])

asymptomatic clinically healthy population. In Averill and Lamb's large sample[29] of 67,375 U.S. Air Force flying personnel, the incidence of abnormal T and S–T segment changes increased from 5.2/1,000 at ages 20 to 24 to 19/1,000 at ages over 45 years. It is recognized that ST–T wave changes may be due also to other causes than latent coronary insufficiency, but these are less likely to show a pronounced age trend. Myocardial infarction was suspected in 0.3 subjects/1,000 at ages 20 to 24 years, increasing to 4.4/1,000 at ages over 45 years.

Prevalence of coronary disease in different populations: It is a reasonable assumption that the prevalence of latent asymptomatic coronary atherosclerosis corresponds to the prevalence of clinical coronary heart disease. There are significant differences in the prevalence of coronary heart disease in different populations, largely parallel to the intake of saturated fats.[7,8] Comparison of electrocardiographic age trends in populations with high and low prevalence of coronary heart disease is therefore pertinent to this problem.

In a quantitative comparison of numerous electrocardiographic items in young (18 to 28 years) and older (45 to 55 years) men in Minnesota (high prevalence) and Italy (low prevalence), the age differences were smaller in the Italian sample, and did not reach statistical significance. In contrast, they were highly significant in the Minnesota sample.[30]

Similar results were obtained in a comparison of age differences between large samples of American and Japanese men.[12] Table V shows the age differences of 4 selected representative electrocardiographic items. The age differences in the Japanese sample are smaller or absent. The prevalence of coronary heart disease is significantly lower in Japan than in the United States.

Table VI shows 7 selected, representative electrocardiographic items in 15 patients with angina pectoris and normal resting electrocardiogram and 233 normal older men.[30] The differences between these groups are similar to age differences of normal men; that is, the amplitudes in the group with angina pectoris are smaller, and the left axis shift is more pronounced. Coronary artery disease exaggerates the normal age trends as long as the resting electrocardiogram is normal. This relationship is obscured by the development of electrocardiographic abnormality in later phases of the disease.

Results obtained by Blackburn et al.[17] in clinically healthy Greek, Italian and American population samples are at variance. There was a significant age trend of amplitudes and axis in these samples, but no significant differences between them in spite of significantly different prevalence of coronary artery disease (low in Italy and Greece, high in the United States). The age groups investigated were small, ranging from 38 to 50 subjects, which may explain the discrepancies, as emphasized previously. However, it is believed that the bulk of the evidence supports the concept of a relationship between normal electrocardiographic age trends and prevalence of latent coronary artery disease.

TABLE VI

Means (M) and Standard Deviations (SD) of Selected Electrocardiographic Items in 15 Patients (P) with Angina Pectoris and Normal Resting Electrocardiogram Compared to 233 Normal Older Men (O)

	R Wave in Lead II (mm)	T Wave in Lead I (mm)	T Wave in Lead II (mm)	ΣT (mm)	QRS Axis (°)	T Axis (°)	T Wave in Lead V_4 (mm)
Group P							
M	7.05	1.71	1.46	3.93	11.00	16.67	3.61
SD	3.79	0.87	0.77	1.35	29.86	33.13	2.24
Group O							
M	7.75	2.01	2.26	5.20	37.77	32.87	7.08
SD	3.16	0.89	0.95	1.74	34.67	23.96	2.49
Δ	−0.70	−0.30	−0.80‡	−1.33‡	−26.77‡	−16.20‡	−3.47†

† $P \leqq 0.05$.
‡ $P \leqq 0.01$.
(Condensed from Simonson.[30])

Predictive value of electrocardiogram: Assuming a relationship between electrocardiographic age trends and asymptomatic coronary atherosclerosis, a predictive value of the resting electrocardiogram in young people for later development of coronary heart disease may perhaps be expected: Are young adults with low amplitude of ventricular complexes and left axis deviation more prone to have coronary insufficiency? Nevertheless, the prognostic value of the resting electrocardiogram for the individual person is poor.[2,17] It should be kept in mind that the age trends were established in large samples, and the wide normal age-corrected range limits are valid for clinically healthy people.

The factors that trigger the development of clinical coronary heart disease are largely unknown for the individual person. In extensive epidemiologic studies risk factors have been statistically identified[2,7,8] but are not revealed in the resting electrocardiogram. Even gross electrocardiographic abnormalities (conduction defects, bundle branch block, abnormal T waves) detected at age 24 years had no predictive value for later morbidity or mortality.[2]

Age Trends in the Exercise Electrocardiogram

The diagnostic value of an ischemic response (sloping down or horizontal S–T depression, types D and E, Fig. 8[31]) for recognition of latent coronary insufficiency and for prediction of mortality has been firmly established.[32,33] A junctional type of S–T segment depression (types B and C, Fig. 8) or isolated T inversion (type F) had no prognostic value.[32,33]

One would expect that the prevalence of an ischemic S–T depression in an exercise test corresponds to the prevalence of coronary heart disease. This is indeed the case. Table VII compares the prevalence of ischemic S–T depression in U.S. railroad clerks and Italian and Yugoslavian farmers. The incidence of ischemic S–T depression is highest and the age difference is largest in American railroad clerks, and lowest in Yugoslavian farmers, corresponding to the incidence of coronary heart disease.[34]

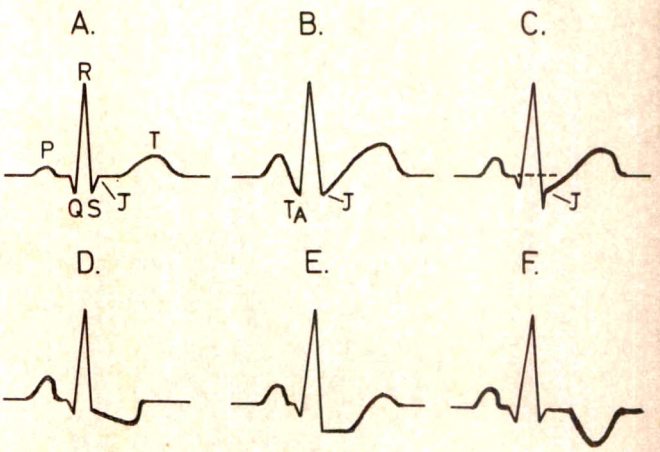

Figure 8. Types of ST–T changes. **A,** normal electrocardiogram, at rest. **B,** false junctional S–T depression, due to atrial T wave Ta. **C,** true junctional S–T depression; **D,** ischemic S–T depression, sloping down. **E,** ischemic S–T depression, horizontal. **F,** isolated T wave inversion. The resting electrocardiogram is normal. (Reprinted from Simonson.[31])

The age difference of the S–T depression was significant for the U.S. railroad clerks, but not for the Italian and Yugoslavian farmers. In the age group 40 to 49, the difference between American railroad clerks and Yugoslavian farmers was significant ($P \leqq 0.05$) but not between American railroad clerks and Italian farmers. For the older age groups, the differences between American railroad clerks and both Italian and Yugoslavian farmers were significant ($P \leqq 0.01$ and $P \leqq 0.001$, respectively).

Taylor and co-workers[35] have compared the incidence of ischemic postexercise S–T depression in sedentary and physically active men (Table VIII). In both age groups, the incidence of S–T depression is significantly higher in sedentary population, corresponding to higher prevalence of coro-

TABLE VII

Prevalence Rates of "Ischemic-Type" ST-T Depression (Minnesota Codes 11, 1, 2, 3) in the Postexercise Electrocardiogram (None at Rest) by Age and Population Group (Rates per 1,000 Men)

Population Group	Ages 40–49 Years		Ages 50–59 Years	
	Total no.	Prevalence Rate	Total no.	Prevalence Rate
American railroad clerks	349	59.5	498	120.1
Italian farmers	369	52.5	347	65.3
Yugoslavian farmers	284	28.9	415	43.2

(Reprinted by permission from Blackburn.[34])

TABLE VIII

S–T Segment Depression >0.5 mm After 3 Minutes of Walking (Clinically Unselected Railroad Employees)

	Sedentary (no. = 763)		Physically Active (no. = 771)	
	A	B	C	D
Age (yr)	40–49	50–59	40–49	50–59
Incidence (%)	5.4	8.2	2.2	2.8
Difference	A vs. B: t = 2.17, P = 0.05			
	C vs. D: t = 0.75, n.s.			
	A vs. C: t = 3.28, P = 0.01			
	B vs. D: t = 4.64, P = 0.001			

(Condensed from Tables 14 and 16, with addition of statistical evaluation. Reprint by permission from Keys et al.[7])

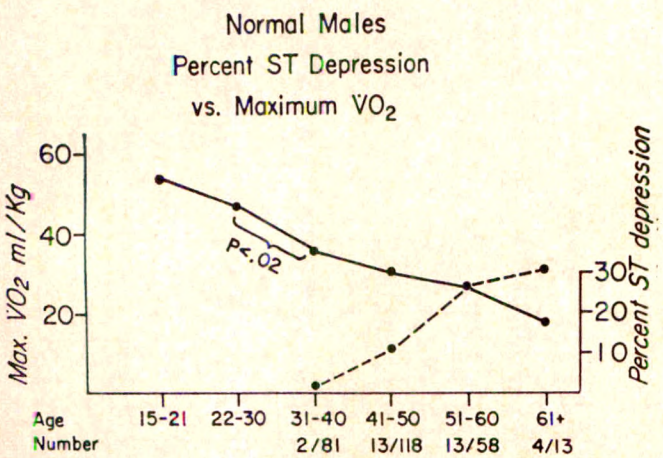

Figure 9. Relationship of the rising age-specific prevalence of S–T segment depression to the maximal oxygen intake ($\dot{V}O_2$) of healthy men. Note the significant decrement in mean oxygen intake in the years prior to the appearance of S–T segment depression. (Reprinted by permission from Bruce et al.[38])

nary artery disease. The age difference is significant in the sedentary men, but not in the active men.

Bruce et al.,[36] by a progressive exercise test with increasing load to maximal capacity, compared middle-aged American and Chinese asymptomatic men living in Taipei, the latter subdivided into 2 groups of upper and lower socioeconomic status. The incidence of significant S–T depression corresponded to the incidence of coronary heart disease (highest in American men, lower in Chinese men of upper socioeconomic status and lowest in Chinese men of lower socioeconomic status). The differences between Americans and both groups of Chinese men were highly significant ($P < 0.01$).

The first observation of age trends in the electrocardiographic response to fairly strenuous exercise was made by Rumball and Acheson[37] in Royal Air Force personnel. The incidence of significant S–T depression increased from 1.4 percent (at ages 19 to 29 years) to 7.1 percent (at ages 45 to 54 years).

Exercise electrocardiogram in men vs women: Åstrand[38] compared age trends of significant S–T depression in the exercise electrocardiogram in men and women. The age trend is similar, but in all age groups the frequency is higher in women. A significant greater frequency in women was found also by other investigators (reviewed by Simonson[39]). This is puzzling because prevalence and mortality from coronary heart disease is lower in women than in men. It has been suggested that coronary atherosclerosis may be more widespread, but less fatal in women, or that the adrenergic discharge is greater. It was pointed out that different normal standards must be used for different ages and for men and women.[6] Åstrand[38] as well as other investigators used the same criteria for men and women for the response to exercise. It would be more appropriate to determine the normal limits of the postexercise S–T changes separately for clinically healthy men and women from their percentile distributions. This probably will significantly reduce the large number of false abnormal ischemic responses in women.

$\dot{V}O_2$ and exercise electrocardiogram: Figure 9 shows the relationship between maximal oxygen intake ($\dot{V}O_2$) and the frequency of significant S–T depression in a progressive exercise test in healthy men, dependent on age.[36] The decrease of maximal $\dot{V}O_2$ precedes the increase of frequency of S–T depression. The age trend of S–T depression starts after age 40 years, that of the drop of maximal $\dot{V}O_2$ after age 21. Since maximal $\dot{V}O_2$ depends largely on the cardiac minute volume which, in turn, depends on the myocardial oxygen supply, one may conclude that from age 40 the decrease of maximal $\dot{V}O_2$ has reached a level where it becomes critical for the oxygen supply of the heart in an increasing number of persons with advancing age.

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Seminar on

Clinical Application of Techniques to Measure Blood Flow in Man. Part I

ALBERTO BENCHIMOL, MD, FACC, Guest Editor

Introduction

ALBERTO BENCHIMOL, MD, FACC

Phoenix, Arizona

This seminar was organized with the idea of providing a survey of recent advances on techniques that are currently being used to determine blood flow in man. Most investigators and physiologists will agree that determination of flow is one of the most important measurements of cardiovascular function, particularly when this measurement is integrated with appraisals of cardiac pressure and ventricular volume data. In recent years we have observed a vigorous effort by many to develop new approaches for determining flow in man with use of well established techniques that have been applied to dog experimentation. It is becoming quite clear that there is an urgent need for methods to measure phasic, continuous, instantaneous volume flow or velocity of flow in the cardiac chambers and major vessels without exposure of the circulatory bed under investigation. Mean flow, regional distribution of flow and total organ perfusion determinations are equally important, particularly when these techniques can be used without the need for cardiac catheterization.

This seminar was organized with these ideas in mind, and the primary objective is to provide cardiologists and internists with an up-to-date concept of what is being accomplished in these areas.

The first paper in this seminar, "Techniques to Measure Coronary Blood Flow in Man," by Bing and co-workers describes the use of radioisotopes for study of the coronary circulation. Bing's past and current work has been outstanding. He has pioneered the development of methods to study the coronary circulation in man dating back to the use of nitrous oxide methods. His current experience with measurement of myocardial microcirculation is intriguing and provocative. In his paper, "Velocity and Flow Measurements by Electromagnetic Techniques," Stein describes his experience with the use of the electromagnetic flowmeter to determine phasic flow measurement, work which is of great practical significance.

Ganz and Swan describe the use of a thermal dilution approach to study ventricular performance; the reader will find most useful information in this paper, "Measurement of Blood Flow by Thermodilution." Theirs is a relatively simple technique that will yield a great deal of information.

Finally, in a paper, "Clinical Application of the Doppler Ultrasonic Flowmeter," our own group describes clinical use of a well established technique to measure phasic, continuous, instantaneous measurement of blood flow velocities in man in a variety of clinical states.

Although there are inherent limitations and advantages of each technique described, it appears that each has its own clinical merits. It is hoped that this seminar, which will appear each month through April 1972, will stimulate other investigators to continue exploring the many facets of, and other new approaches to, measurement of phasic blood flow in man.

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Techniques to Measure Coronary Blood Flow in Man

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This paper presents a review of current techniques to measure coronary blood flow in man. Emphasis is placed on methods utilizing diffusable gases, diffusable substances, continuous thermodilution and ultrasonic Doppler flowmeter. The advantages and disadvantages of each method are enumerated, and the general purpose of measuring coronary blood flow in man is discussed.

During the last 20 years, attempts to measure coronary blood flow in man have made considerable progress. The impetus for this work has primarily come from efforts to measure cardiac metabolism and to gain insight into the dynamics of the coronary circulation in health and disease. These aims cannot be accomplished with methods generally employed in animals unless the patient's chest is opened. The methods to be discussed in this report will be primarily concerned with those applicable to patients. In principle, those methods can be divided into (1) methods utilizing diffusable gases; (2) methods utilizing diffusable substances that actively enter the cell; (3) measurement of coronary sinus blood flow by continuous thermodilution; and (4) methods to measure phasic coronary blood flow in man by means of an ultrasonic Doppler flowmeter. Other procedures described recently, such as coronary blood flow measurements through single coronary arteries by Roentgen densitometry or Anger camera technique, are still in the experimental stage and will not be discussed here.

Methods Using Diffusable Gases

Diffusable tracers or gases can be used for calculations of total flow based on the Fick principle. The Kety-Schmidt technique,[1] used extensively for the measurement of total cerebral or myocardial blood flow with N_2O gas as an indicator, is a specialized application of the Fick principle.[2] Blood flow can be measured by means of a substance that accumulates or leaves the region to be studied. With use of the Fick principle, at equilibrium the tissue concentration equals the venous concentration times the blood-tissue partition coefficient. The arteriovenous concentration difference is determined during the period of saturation or desaturation after cessation of nitrous oxide breathing.

To apply this principle, one must collect mixed venous blood from the region that drains the heart muscle. It is also necessary to know the time required for the tissues to reach equilibrium with venous blood. Regions that do not drain into the venous outflow will not contribute to the flow measurement. The procedure for total coronary blood flow has also been utilized using substances such as ^{131}iodine, antipyrine,[3] ^{75}krypton, ^{85}krypton,[4,5] and argon.[6] It is important to realize that these procedures are based

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on concentration of indicator in the venous blood from the region to be studied and include flow passing through the total capillary beds, including both nutritional as well as shunt flow (blood passing directly from arteriole to venous channels without permitting tissue exchange). Therefore, these substances measure total regional blood flow. One of the major difficulties in measuring coronary blood flow with diffusible gases is the effect of nonhomogeneous perfusion of the heart muscle. In such a case, the arterial and coronary sinus concentrations do not come into equilibrium within the period of measurement (5 to 6 minutes). It is difficult to assess this error quantitatively.

Nitrous oxide method: Historically, the nitrous oxide method was one of the first procedures to be utilized for the determination of coronary blood flow in man.[7] Certain valid theoretical objections have been raised against the method. The assumption of flow homogeneity throughout the heart had been earlier questioned: this has been confirmed by Hershgold et al.[8] at least for the rat heart. Further, distribution of left coronary arterial flow has, except for a small percentage, been established as left ventricular.[9] The coronary sinus drains primarily left ventricular muscle so that one only measures the blood flow through a unit of weight of this particular region. The principal practical disadvantages of the nitrous oxide method for measuring coronary blood flow are 2-fold: First, one cannot perceive rapid changes in coronary blood flow; therefore, reliable data cannot be obtained on patients who are not in a steady state. The method must be carried out for a minimum of 4 minutes until equilibrium of the heart muscle with nitrous oxide has been accomplished. Second, although coronary sinus catheterization is not hazardous, it involves careful, time-consuming preparations and some inconvenience to the patient. In addition, although in our first published report[7] the difficulties of intubation of the coronary sinus were overrated, the procedure although feasible in most patients cannot be accomplished in some due to anatomic variations.

The most pertinent results obtained with the method are the following: Coronary blood flow in patients with arteriosclerotic heart disease may be normal[10,11]; coronary vascular resistance is increased in hypertension[11]; total coronary blood flow for the hypertrophied heart is increased although the flow per unit of tissue is normal[11]; and, finally, although the coronary flow is normal in patients with coronary artery disease, the response of the coronary circulation in these patients to coronary vasodilators is different from that of normal individuals.[12,13] Another finding is a marked increase in coronary flow in patients with a large arteriovenous fistula or coarctation of the aorta. Unquestionably the greatest use of coronary sinus catheterization is in conjunction with the determination of myocardial metabolism in man.[14] However, this subject is beyond the scope of the present discussion.

Methods Utilizing Diffusable Substances That Actively Enter the Cell

Among these substances are ^{86}rubidium, ^{84}rubidium, ^{42}potassium and ^{24}sodium. The clearance of these substances measures only nutritional blood flow. However, these tracers can also be used for the measurement of total flow if the Fick principle is applied. Studies on isolated skeletal muscle have demonstrated parallel qualitative changes in the extraction of ^{86}rubidium and oxygen after nerve stimulation or the administration of vasoactive agents.[15,16] The factors involved in the exchange of these substances between the blood and tissues are (1) rate of capillary flow, (2) capillary surface area, and (3) permeability of the capillary and cell membrane.[15,17,18] When the blood-tissue permeability is great in comparison to blood flow, the exchange between the blood and tissues is essentially a flow-limited process and can be used as an estimate of local nutrient circulation.[17–19] This applies if one assumes that permeability is not limited and that constant clearance of the tracer is a function of the volume of capillary blood flow available for exchange.[17]

The tracers named are all lipid-insoluble substances. It is possible that they become diffusion-limited at high flow rates and do not faithfully predict local tissue flow under certain conditions.[19,20] The validity of the use of these substances is based on the premise that the uptake or removal of tracers is a blood flow-dependent process. It is likely that membrane permeability to most tracers is not limiting but that nonhomogeneity of a tissue can influence the results. There are other limitations to the use of these tracers. With use of ^{42}potassium or ^{84}rubidium, it is important to establish that a change in potassium flux does not influence the uptake. Efflux of potassium or rubidium from the cell should be slow and should not be significantly influenced by changes in blood flow rates.[17] However, the latter hypothesis has not been established with certainty. Other main factors that can impair the validity of these tracer methods are cell injury, which changes cellular permeability, and the effect of gradual saturation of the tissues, which can occur with prolonged administration of the tracer. It has been shown that prolonged exposure to ^{84}rubidium with a rise in tissue level will result in a gradual decline in the extraction ratio with time.[12] This only occurs with infusion but not with a "slug injection" of the isotope with short periods of exposure to the tracer.

Therefore, flow as measured by means of rubidium clearance reflects only that portion of the total blood flow which is effective in blood-tissues

exchange of rubidium. Since rubidium is exchanged only in the capillaries, flow passing through non-nutritional channels is not measured.

Subsequent to the initial studies by Love et al.[21] using ^{86}rubidium and ^{42}potassium to ascertain myocardial blood flow, radioactive rubidium isotopes, which are handled metabolically by the tissues in a manner similar to potassium, have been widely used for evaluation of myocardial blood flow using either direct or external counting techniques.[12,22,23] The positron emitter ^{84}rubidium and a double coincidence counting system for external measurement for myocardial ^{84}rubidium uptake were introduced by Bing et al.[12] At the onset, a constant infusion of rubidium was employed, but calculations necessitated computers and were difficult to carry out. More recently the determination of coronary blood flow has been accomplished with a bolus injection of ^{84}rubidium. The single injection of isotope in the measurement of coronary blood flow using ^{86}rubidium was first introduced by Donato et al.[24] followed by Knoebel et al.[25]

Since ^{84}rubidium is a positron emitter, it was chosen because one may be able to separate myocardial radioactivity from activity present in surrounding tissues from the chest wall and from the activity of blood in the cavities of the heart. Extensive collimation is not necessary.[20] Only arterial and venous punctures are necessary for the measurement of nutritional blood flow. For the calculation of total blood flow, the coronary sinus must be intubated. The double coincidence counting technique, which is necessary for determination of coronary nutritional and total blood flow with ^{84}rubidium, has been extensively described in previous reports from this laboratory.[12,20,26] It should be mentioned that allowances must be made for chest thickness, background activities and differences in efficiency between the coincidence and the well counter.

Fractional distribution of rubidium: The method for measuring effective capillary blood flow by means of a bolus of ^{84}rubidium is based on the principle of fractional distribution of rubidium after a single intravenous injection of this substance.[27] In principle, the fractional distribution of rubidium in various regions corresponds to the fractional distribution of the cardiac output. It is valid if the extraction ratio of the indicator by the organ under study is the same as the overall extraction ratio of the body. Sapirstein[27] found that the extraction ratio is not unity but that up to 40 percent of the injected dose of rubidium recirculates. He suggested that the myocardial extraction ratio of rubidium equals total body extraction ratio during a period of several recirculations up to 120 seconds after injection of the isotope. Rubidium reenters the blood from the tissues very slowly. This accounts for the fact that uptake by the heart remains a constant fraction of the cardiac output.[16,22] The formula for measurement of effective capillary blood flow (ECF) has been described in numerous publications from this laboratory.[12,20,26]

Coincidence counting method: This method, using ^{84}rubidium, was developed over a period of almost 10 years. Although the test itself is easy to carry out, it needs continuous monitoring, standardization of the ^{84}rubidium source and calibration of the instrument. The design of the original coincidence counting instrument has been considerably simplified, and its use at the bedside is now possible (Co-Nuclear Co., Winnipeg, Canada). The differentiation between total and nutritional flow with this technique is theoretically a valid assumption. The question as to what constitutes shunt flow as compared to overall flow has been recently dealt with in a paper from this laboratory describing the coronary capillary microcirculation.[28]

In general, the data when carefully collected show a good correlation between total flow and effective coronary flow under control conditions. Some pertinent results obtained with this technique concern the effect of drugs on the coronary circulation. It was found, for example, that infusion of norepinephrine or nicotine increases total coronary flow to a larger extent than nutritional coronary blood flow.[20] Isoproterenol, on the other hand, causes a proportionate increase in total and nutritional coronary blood flow. The difference in response of the effective coronary flow to isoproterenol and norepinephrine cannot be explained by the flow dependency of ^{84}rubidium extraction. Since membrane and capillary flow permeability and available capillary surface area determine the extraction ratio of rubidium and, thus, the effectiveness of capillary flow, the different responses to the norepinephrine and isoproterenol can be explained either by a specific action of these drugs on the permeability of capillary or cell membranes or by an effect on capillary flow. Winbury[16,29] and Renkin[30] and their co-workers, by measuring clearance of ^{86}rubidium at constant flow rates in skeletal muscle in dog heart, showed that norepinephrine has an effect on precapillary sphincters which regulate capillary surface area.

The method also has confirmed a dichotomy in the response of the coronary circulation in normal as compared to atherosclerotic coronary arteries. This was first observed with reference to nitroglycerin[23,31] and was later extended by Knoebel et al.[32] to isoproterenol. Rickart et al.[33] confirmed these findings in animals with and without restriction of coronary flow induced by ameroid rings placed around the coronary arteries of the dog. Other studies in patients with acute myocardial infarction demonstrated a significant decrease in effective coronary flow within 4 days of infarction. The low flow persisted in 1 patient 6 weeks after the initial injury.

Since the method is based on Sapirstein's principle, it follows that the extraction ratio of ^{84}rubidium by the body and by the heart must be equal during the period of observation under all conditions. Little information is available on the equality of the extraction ratios of the heart and body when a portion of the myocardium is infarcted.

Precordial radioactivity method: Mention also should be made of determination of myocardial blood flow in man by the determination of precordial radioactivity after the injection of solutions of radioactive gas directly into the coronary arteries. Direct injection into the coronary arteries is necessary in these instances, since otherwise it is not possible to separate the activity of the heart from that of surrounding structures. The advantages of the method are that one is able to separate flow through the right and left coronary circulations and that flow values can be directly correlated to the anatomic findings obtained on coronary arteriography. Gases used are ^{85}krypton and ^{133}xenon. As with nitrous oxide, one determines total coronary blood flow with these gases. In man, ^{133}xenon is preferred.[5]

Measurement of Coronary Sinus Flow by Continuous Thermodilution

Dye-dilution or thermodilution procedures in the measurement of coronary sinus flow have been employed by a number of investigators.[34,35] Using dye-dilution methods, Nakamura et al. insert a catheter into the coronary sinus and a polyethylene tube through the catheter, which then protrudes from the tip of the coronary sinus catheter into the coronary sinus. An indicator (indocyanine green) is then injected through the polyethylene tube at a constant rate. Coronary sinus blood is drawn through the catheter and dye concentrations of the plateau in the dye concentration are measured. Coronary sinus flow can then be calculated. These authors[35] believe that the method is reproducible in spite of positional changes of the coronary sinus catheter.

Ganz et al.[34] used a similar principle but employed thermodilution instead of the indicator dye. They used a specially designed catheter (Wilton Webster Manufacturing Company, Altadena, Calif.) for the measurement of coronary sinus blood flow. In the lumen of the catheter, separated by a thermically insulating space of air, a Nylon® tubing serves for injection of indicator. It is constricted distally to an injection orifice. A thermistor is mounted on the shaft of the catheter 10 to 15 mm proximal to the injection orifice. A second thermistor lies inside the Nylon tubing close to the injection orifice to measure the temperature of the injectate just prior to its mixing with the bloodstream. Temperatures are measured with thermistors. A large volume capacity pump was used for injecton of indicator.

Normal values obtained for coronary sinus blood flow ranged between 83 and 158 ml/min (mean 123 ml/min). The mean coronary sinus flow is 70 ± 14 ml/min. As is to be expected, there was no difference between normal values and those obtained in patients with coronary artery disease. Certain limitations must be kept in mind. In the first place, good mixing of blood with the injectate is the basic assumption for the accuracy of the method, as it is for all procedures of dilution. This can be obtained at relatively high rates of injection of the indicator. The question must also be raised as to what extent coronary sinus blood flow represents perfusion of the left ventricular myocardium. It has been stated by Rayford et al.[9] that in dogs 75 to 95 percent of left coronary arterial flow is recovered in the coronary sinus and that the ratio remains reasonably constant under various hemodynamic conditions. Anatomic studies have shown that the left ventricle is drained primarily by the coronary sinus. The method necessitated coronary sinus catheterization with the accompanying minor discomfort to the patient and major preparations for the laboratory. Advantages are that the equipment is simple and inexpensive and that the procedure can be carried out in conjunction with other cardiac catheterization procedures.

Methods to Measure Phasic Coronary Blood Flow in Man by an Ultrasonic Doppler Flowmeter

This method is based on the Doppler principle as formulated by Franklin[36] and by Benchimol[37] and their co-workers. In principle, measurements are carried out by means of a Doppler catheter flowmeter, constructed according to the technique described by Benchimol. Two hemidiscs of piezoelectric crystals are used. They are mounted at the end of a cardiac catheter which is connected to the Doppler ultrasonic flowmeter-telemetry system. Velocity of blood is measured according to the Doppler shift principle. A high frequency sound from 1 crystal hemidisc is beamed to the blood passing through the vascular lumen around the catheter. That portion of the emitted sound which is back-scattered by blood particles is detected by the other crystal hemidisc. The reflected signal differs in frequency from the original or incident signal by an amount proportional to the velocity of the target, in this instance the blood cells. Thus, the frequency of the backscattered sound is proportional to blood velocity. By use of a magnetic tape, the output of the audio signal and of the converted analog record can be recorded. By taking a fixed

frequency from a signal generator and applying it to the input of the frequency to voltage converter, the record can be calibrated. Blood velocity is then computed by the Doppler shift formula.[36,37] Calibration is accomplished by obtaining zero flow velocity by briefly interrupting the input signal through the frequency meter, since zero frequency shift corresponds to zero velocity. It should be pointed out here that the method does not measure blood flow but rather blood velocity. Details of the method can be obtained from the papers by Benchimol[37] and Franklin[36] and their co-workers.

The advantage of the procedure is that phasic blood velocities can be measured in man using either a transcutaneous approach or probes surgically implanted around the blood vessels. With this method, Benchimol et al.[38] have measured right ventricular blood velocity in man and have recently been able to record phasic coronary blood velocity as well.[39] The latter has been accomplished by placing the tip of the Doppler catheter at the ostia of both or either of the coronary arteries where measurements were made. The technique used to position the catheter at the ostia of the coronary arteries is essentially the same as that used for selective coronary arteriography.

Coronary blood velocity: Using this procedure, Benchimol et al. demonstrated the feasibility of obtaining continuous measurement of instantaneous phasic coronary blood velocity in man. In general, the velocity wave pattern agrees with the observation of others[40] made in animals in which electromagnetic or ultrasonic flowmeters were inserted for long periods. At the onset of isovolumic contraction, there is an abrupt decrease in coronary blood velocity. As the level of aortic pressure rises, coronary blood velocity increases rapidly to a relatively low peak and decreases again during the period of slow ventricular ejection. With the onset of isovolumic relaxation, blood velocity increases rapidly, peaking early in diastole at the time of rapid ventricular filling. This peak is of short duration; then the velocity tracing progressively returns toward the base line to reach its lowest point at the end of atrial systole. Velocity patterns were not different in patients with coronary artery disease, except in 1 patient with near total occlusion of the proximal segment of the right coronary artery, in whom, close to the occlusion, the velocity pattern was continuous throughout the entire cardiac cycle due to a large increase in the systolic fraction. Benchimol[39] considers that an increase in blood velocity during systole is an important compensatory mechanism in patients with severe perfusion deficit due to coronary artery disease. Using their method, Benchimol et al.[39] found that nitroglycerin increases coronary blood velocity both in normal persons and in patients with coronary arteriosclerosis.

The main limitation of the technique is the need for correct positioning of the catheter tip. If the catheter tip lies against the wall of the aorta or coronary artery, adequate velocity signals can be obtained in only 70 percent of patients. Blood flow measurements cannot be made unless the cross-sectional area of the coronary artery is known. Finally, the technique is based on an invasive procedure. Unquestionably the main advantage of the technique is that phasic measurements of coronary blood velocity in man are a feasible tool.

Conclusions

In the foregoing discussion, various clinically applicable methods for the determination of coronary flow have been discussed. Each possesses individual advantages and disadvantages.

The nitrous oxide method demands a prolonged steady-state and catheterization of the coronary sinus, and it determines *total* coronary flow for a unit of left ventricular muscle. Its greatest advantage lies in its use in combination with the study of cardiac metabolism. The coincidence counting method, utilizing the positron emitter ^{84}rubidium, permits determination of both nutritional and total coronary blood flow. Catheterization is not required for the former. Its accuracy depends on the validity of the fractional distribution principle and on the fact that coronary flow and not cell permeability must be rate-limiting.

The chief difficulty of methods utilizing dye or thermodilution principles lies in obtaining adequate mixing between the point of injection and sampling. Here, too, as in the nitrous oxide method, the question of the area drained by the coronary sinus is pertinent, and catheterization of the coronary sinus is essential. By utilizing the Doppler principle, one can obtain phasic changes in coronary flow in man. The method necessitates catheterization of the ostia and measures blood velocity rather than flow.

One may ask a final question: Why all the effort to measure coronary blood flow in man? It is true that the clinical and diagnostic value of the determination of coronary flow is still limited, as compared to direct visualization of coronary arteries by angiography. However, it is likely that the tests based on the different response of the coronary circulation to nitroglycerin or isoproterenol reveal changes in functional response of the coronary circulation. The greatest benefit from these measurements is derived from fundamental insight gained in the behavior of the coronary circulation. These studies, together with those carried out on the coronary microcirculation, are bound to influence basic and clinical concepts concerning ischemic heart disease.

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Part Two of this seminar will appear in the February issue.

Prospects in Antithrombotic Therapy

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Currently there is an increasing awareness of the magnitude and scope of the problem of thrombosis; renewed interest in this lesion also has been spurred by better appreciation of the limitations inherent in the use of the available anticoagulant agents as well as developments in new forms of antithrombotic therapy. Surprisingly, concern over coronary artery thrombosis as a proximate event precipitating acute myocardial infarction has not received the attention it deserves even though the most recent studies indicate that a thrombotic episode occurred in approximately 90 percent of patients who died after a classic acute myocardial infarction. This article briefly reviews (1) current concepts of the pathogenesis of acute coronary thrombosis; (2) the basis for, and developments in, the use of anti-platelet aggregating agents for prophylactic purposes; and (3) prospects for the application of thrombolytic agents to the treatment of acute myocardial infarction.

The eradication of cancer, which is receiving much publicity lately, is a most laudatory objective for this decade, but more important from a public health standpoint is the solution of the problem of occlusive disease of the arteries. The latter remains the number 1 health hazard facing the aging population of the Western world, afflicting probably more than 2 million persons a year in the United States alone and likely to grow in incidence and numbers as longevity increases. Most important in this regard is acute myocardial infarction since it is estimated that this complication will be suffered by more than 1 million persons this year.

Arterial occlusive disease is most often related to atheromatous involvement of the vessel; therefore, concern over this lesion is well justified, and its control undoubtedly will have a far-reaching impact on morbidity and mortality. However, occlusive disease of the arteries is usually a mixture of atherosclerosis and thrombosis and, while the relative contribution of each and the relation between them remain unsettled, most pathologists agree that the decisive acute occlusive events that precipitate major pathologic sequelae are usually thromboembolic in nature. Accordingly, it is encouraging to note that the thrombosis problem is beginning to receive the attention it deserves. In this respect, it is rewarding to see the leadership being exerted by the major "heart" oriented organizations: The National Heart and Lung Institute is creating several multidisciplinary Thrombosis Research Centers; the American Heart Association has established a Council on Thrombosis; and the American College of Cardiology has demonstrated its involvement through superb educational programs and in affording me the opportunity to give this Founder's Lecture.

From the Department of Medicine, Temple University School of Medicine, Philadelphia, Pa. This work was presented as the Founder's Lecture, American College of Cardiology, Twentieth Annual Meeting, Washington, D. C., February, 1971.

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TABLE I

Newer Studies on Prevalence of Thrombotic Coronary Artery Occlusion in Patients Dying After Myocardial Infarction of Recent Origin

Source	Prevalence of Thrombotic Occulsion (%)
Mitchell and Schwartz (1963)[1]	88
Harland and Holburn (1966)[2]	91
Davis (1970)[3]	96

Coronary Artery Thrombosis in Myocardial Infarction

Considering the renewed interest in thrombosis, it is quite surprising that concern over coronary artery thrombosis has not received the attention it deserves. Lack of interest in coronary thrombosis probably reflects a changing attitude concerning the importance of this lesion in the pathogenesis of acute myocardial infarction. Two decades ago, the term acute coronary thrombosis was used almost synonymously with acute myocardial infarction; today the terms are used independently, and rarely does the physician attempt to identify the proximate event leading to the infarction and, when he does, thrombosis no longer appears to have the prominence it once enjoyed. Undoubtedly this changing attitude is based on pathologic observations that indicate that acute thrombi are infrequently found in patients dying suddenly of a "heart attack," and on the argument that, when thrombi are found in patients with proved myocardial infarction, they represent an effect of the infarct rather than its cause. Let us analyze these aspects further.

Most of the confusion over incidence arises from difficulties in case selection and in the methods of pathologic examination: In many of the studies, all cases of sudden death were included with the more classic myocardial infarctions and, when the vessels were examined, they were either cut longitudinally, which is an excellent method for dislodging thrombi, or sectioned horizontally at several sites but far enough apart to overlook small thrombi.

Recent observations on sudden death (within an hour of onset of symptoms) indicate that most of these fatalities probably arise from an acute arrhythmia, not from a myocardial infarction; that is, the latter is not the usual cause of sudden death. Therefore, it is not surprising that the incidence of demonstrable coronary thrombosis is low in this group. When cases of sudden death are eliminated, and examination of the coronary vessels is (1) restricted to patients who die with well documented clinical and pathologic evidence of recent infarction, and (2) carried out with serial sections made every 2 to 3 mm and, when indicated, the vessels decalcified before sectioning, then each of the 3 most recent studies[1–3] (Table I) has demonstrated an incidence of thrombotic occlusion which approximates 90 percent. The thrombi usually occurred at sites of narrowing of the vessel consequent to an underlying atheromatous plaque, and most often were less than 5 mm long, although some extended for several centimeters. The left anterior descending branch was most frequently involved, followed by the right coronary artery and the left circumflex branch. Interestingly, thrombi in the left anterior descending branch usually were found within the first 2 cm of origin, whereas thrombi in the right coronary artery demonstrated no predilection as to site, with some thrombi found as far as 10 cm from the origin of the vessel.

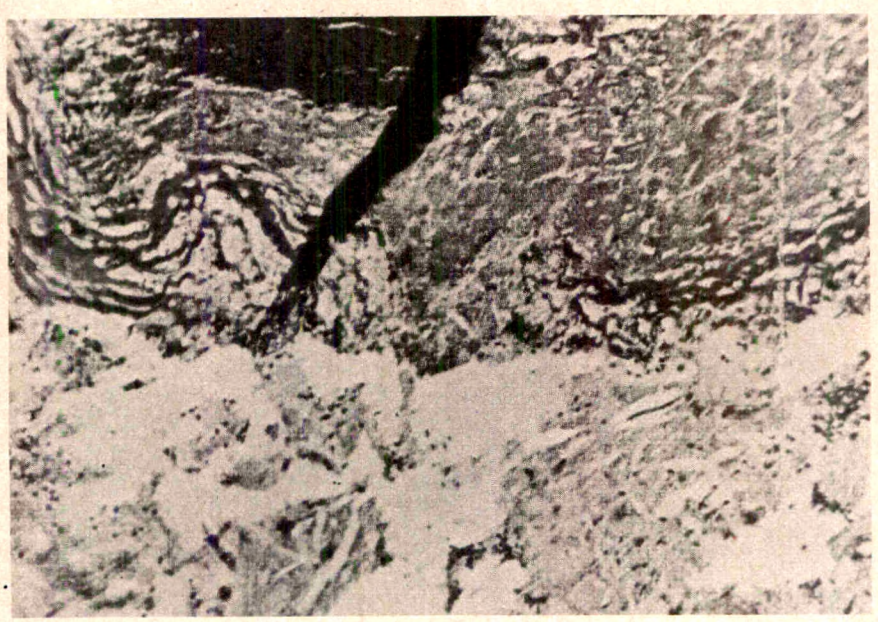

Figure 1. Thrombosis on atheromatous plaque of coronary artery. (Reproduced by permission from Constantinides[4])

Pathogenesis of Coronary Artery Thrombosis

The high incidence of coronary artery thrombosis in patients with unequivocal evidence of acute myocardial infarction does not establish a pathogenetic role for this event, particularly as the suggestion has been made that the thrombosis is a consequence of the tissue necrosis. The latter view is difficult to reconcile with data from the more detailed histologic studies of Constantinides[4] and confirmed by others.[2,5] These investigations established clearly that almost all thrombi were superimposed on and associated with fissures, cracks or ulcers in the intima of atheromatous or fibrosed arterial walls (Fig. 1). Note the mushy atheromatous plaque at the bottom, the break in the fibers of the intimal wall just above it, which is filled with a platelet mass, and, at the top left, a superimposed fibrin-red cell coagulum. These observations have led to the inescapable conclusion that thrombosis in the major arteries of the heart is initiated in most cases by the breaks in the vessel wall although, admittedly, the rate of growth, ultimate size and fate of the thrombus is dependent on other factors, such as platelets, fibrin formation, fibrinolysis and vascular flow. Most convincing in establishing the primacy of the intimal interruption in initiating the thrombosis is that the breaks are covered and filled by platelet masses and that fragments of the atherosclerotic wall, including shreds of collagen, are often buried in the thrombi.

Consequently, although many of the details remain to be elaborated, a useful outline (Fig. 2) has emerged for the pathogenesis of acute coronary thrombosis: For one or more reasons (aging and hardening, trauma from vascular flow or a microhemorrhage in the vascular wall), a plaque or fibrosed vessel wall cracks, exposing the subendothelial microfibrils and collagen of the subintimal tissue; the latter trigger the sticking, aggregation and formation of a platelet mass; this is followed by the release of platelet factors, which results in the deposition of fibrin sufficient to stabilize the platelet mass and also serves to initiate the development of a superimposed fibrin-red cell coagulum. The end result is a typical arterial thrombus which occludes the vessel and leads to severe ischemia, myocardial necrosis and infarction.

Acceptance of this view, which best fits the information available at present, reestablishes the primacy of acute coronary thrombosis as the immediate cause of most cases of acute myocardial infarction and indicates the importance of thrombus prevention as an immediate goal for influencing strikingly the incidence of acute myocardial infarction.

Prevention of Coronary Artery Thrombosis

What are the prospects for the effective prevention of coronary thrombosis other than through the elimination of the underlying atherosclerosis? The long-term use of coumarin compounds, which has been in vogue for many years, does not significantly affect platelet sticking and aggregation to the site of the vascular lesion, and it is the platelet mass which must be prevented if we are to inhibit the formation of a coronary thrombus. Thus, the immediate objective is well defined—to develop agents capable of inhibiting platelet sticking and aggregation to the site of vascular lesions in man.

Platelet anti-aggregating agents: The investigation and development of platelet anti-aggregants has been underway for some time; the prospects look bright for the future, although admittedly much remains to be done. There are many pharmacologically active anti-aggregating agents

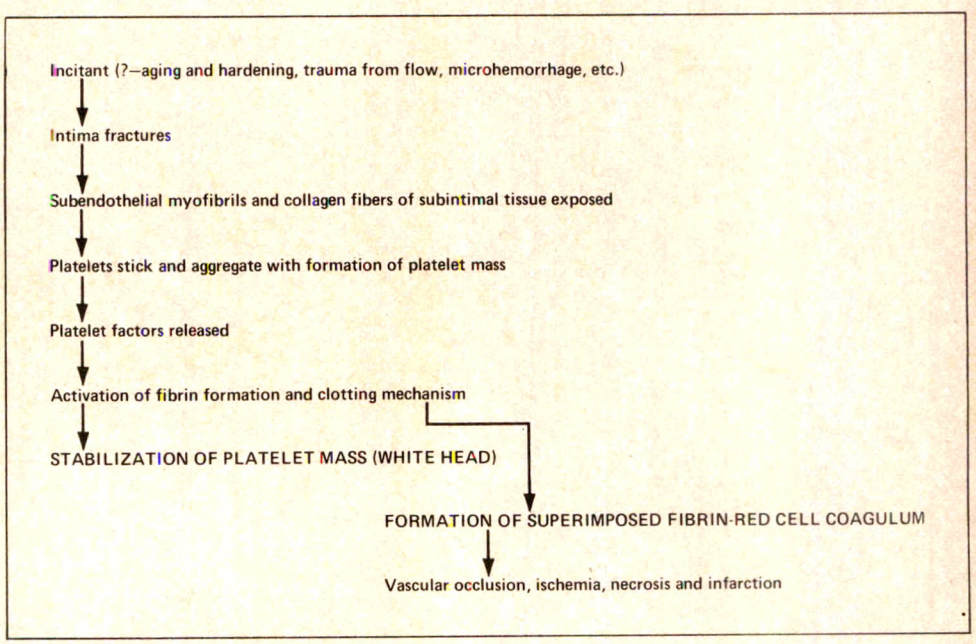

Figure 2. Pathogenesis of acute coronary artery thrombosis.

but 3 have come to the fore (aspirin, sulfinpyrazone and dipyridamole)[6-8]; all have demonstrated an effect in vitro and in experimental animal models and currently are in various stages of clinical investigation. Considering that the in vivo effects of these agents in preventing arterial thrombus formation in man may not correlate too closely with observations on inhibition of platelet aggregation in vitro, or on thrombus prevention in experimental animal models, it would be most helpful if we had available a human disease state in which the pharmacologic effects of the anti-aggregating agents could be screened quickly and under controlled conditions; such information would be most useful before embarking on major clinical trials which will require large numbers of patients and extend over several years.

From a practical standpoint, the most useful model for obtaining quick answers to the in vivo efficacy of an antithrombotic agent would be in the prevention of thrombosis in the deep veins of the lower limb, particularly if this could be combined with a sensitive technique, for example, ^{125}I-labeled fibrinogen scanning to demonstrate early or incipient thrombosis. However, the lesion in this instance is a venous thrombus in which platelet mass formation is unlikely to play a major role. More appropriate would be an arterial lesion; here the 2 most attractive areas for study are embolization from valvular prostheses and transient cerebral ischemic attacks. Although either would be a good model, surgical developments are restricting the availability of suitable patients. New types of artificial valves are being introduced frequently, in an attempt to circumvent thromboembolic and other complications, and for transient ischemic attacks, surgical endarterectomy is being performed to an increasing extent, particularly when significant carotid vascular lesions are demonstrated by angiography. Nevertheless, plans are underway to test the effect of aspirin in reducing the frequency of transient ischemic attacks. Meanwhile, pressures are mounting for the immediate institution of a trial of platelet anti-aggregants in the prevention of coronary thrombosis; such a trial needs to be undertaken, but only when adequate information is at hand to make wise decisions as to the best agent and dosage to employ.

Antithrombotic Therapy in Acute Myocardial Infarction

Anticoagulants

What are the prospects in antithrombotic therapy for patients undergoing an acute myocardial infarction? Although heparin and coumarin therapy have been in common use for many years, experience has taught us that these agents are primarily useful for the prevention of venous thrombotic disease and its complications; they have little value in influencing the formation of an arterial thrombus or its subsequent resolution. As such, they are not designed to have a striking impact on the morbidity and mortality from acute myocardial infarction; their value in this disorder is restricted to thrombus growth in the coronary vessels, and to the prevention of venous thrombosis, pulmonary embolism, mural thrombus formation and systemic embolization. The former does not appear to be an important consideration, and the latter complications account for approximately 6 percent of the deaths. Intensive anticoagulant therapy probably has eliminated half of these, but such a gain represents only a small fraction of the problem of survival following an acute infarct. Pump failure is the most important consideration, and more appropriate for its treatment would be the rapid restoration of blood flow through removal of the occluding thrombus. If the latter can be achieved medically by thrombolytic agents in a simple and reliable manner without undue hazard, the rapid reperfusion of the affected myocardium is likely to salvage some of the dying muscle, improve myocardial function and diminish irritability.

Thrombolytic Agents

At the present time, 2 powerful clot-dissolving agents, streptokinase and urokinase, stand ready to be tested in acute myocardial infarction. These agents, when used in appropriate dosage, have been shown to produce an active thrombolytic state in vivo capable of mediating thrombolysis and, although the clinical experience with each differs markedly, both agents have demonstrated ability to dissolve human thrombi in vivo. Let me briefly summarize the present state.

Streptokinase: The clinical experience with streptokinase already has assumed extensive proportions, sufficient in size and scope to indicate the areas where it is likely to prove beneficial.[9,10] Streptokinase is a secretory protein of hemolytic streptococci and the most widely used laboratory activator of human plasminogen, the naturally occurring fibrinolytic enzyme precursor. It was originally developed for thrombolytic purposes in the United States,[11,12] where it served as a model for establishing the scientific basis and therapeutic potential for the in vivo use of plasminogen activators. The investigation of streptokinase was terminated here in 1960 because of its antigenicity and the tendency for preparations to elicit undesirable and ill-understood pyrogenic reactions. Since the substance could be produced relatively inexpensively and in large quantities, several foreign pharmaceutical firms undertook the further development of streptokinase and it subsequently became commercially available abroad. Pyrogenicity was minimized by the production of more purified preparations, and therapy was streamlined

through the introduction of practical dosage schedules which, when monitored by simple laboratory tests, circumvented many of the difficulties originally encountered here. Although the antigenicity of streptokinase will always impose restrictions on its utility, particularly in the retreatment of persons suffering from recurrent thrombotic episodes, this has not proved to be a deterrent to its clinical acceptance. It is estimated that perhaps 50,000 patients have received streptokinase therapy; most of the experience has been in West Germany, Switzerland, Sweden and Australia, and indications exist that streptokinase is being used in Russia as well. Currently, streptokinase is once again under active study in the United States.

The use of plasminogen activators, like streptokinase, is based on data[13] which suggest that the most sensitive mechanism for thrombolysis involves the diffusion of an activator into the thrombus with conversion of the plasminogen within the thrombus to the active fibrin-dissolving enzyme, plasmin; thus, one of the practical therapeutic questions has been whether local perfusion of an occluded vessel with streptokinase would have advantages over the systemic intravenous administration of the agent. Although this question is not resolved, most investigators agree that systemic intravenous administration achieves as good a result as local perfusion; thus, unless a catheter is already in situ, no need exists for such an ancillary procedure.

Most investigators are now using a fixed dosage schedule, that is, a loading dose of 250,000 units of streptokinase followed by a sustaining infusion of 100,000 units/hour. Although patients vary greatly in their resistance to streptokinase due to the presence of variable amounts of antistreptokinase and other inhibitory substances, this regimen contains sufficient streptokinase to overcome the resistance of approximately 85 to 90 percent of the patient population and maintain free circulating levels of the agent sufficient to induce and sustain an active thrombolytic state. While the latter can be monitored by measurements of circulating fibrinolytic activity, the only test necessary is the thrombin time, that is, the speed of clotting upon the addition of an excess of thrombin to plasma. In the presence of thrombolytic agents, the thrombin time reflects the appearance and accumulation of fibrinogen breakdown products, and indirectly becomes a measure of the activity of the thrombolytic state. Thus, in patients with high resistance, the thrombin time shows little change, suggesting the need for a higher dose; alternatively, an excessive increase in the thrombin time indicates high levels of circulating proteolytic activity and an enhanced risk of bleeding and may call for a decrease in the dose level.

The major hazard with streptokinase, as with other thrombolytic agents, is bleeding; this is most often encountered at the scene of invasive procedures (venous cut-downs, needle sticks, arterial punctures, and others) or at the site of intramuscular injections. Bleeding from these sites is usually controllable by local pressure, but on occasion more serious bleeding may occur into areas of trauma or recent operative wounds. The contraindications for streptokinase are the same as for anticoagulant agents. Other undesirable effects attributable to streptokinase are an occasional severe pyrogenic reaction, rash and, in rare instances, an anaphylactoid-like syndrome.

While investigators have been concerned over the possibility that dissolving clots may embolize, this has not proved to be a significant hazard; thrombi undergoing dissolution progressively shrink in size rather than break up into fragments. The question also has been raised as to whether a prolonged thrombolytic state may be followed by a "rebound" thrombotic state at sites other than that of the original lesion. Short courses of streptokinase therapy—that is, for 24 hours—when followed by adequate anticoagulation have not been associated with unexpected thrombotic events. With longer courses of therapy, new thrombi occasionally have been observed even in the presence of anticoagulation; however, the significance of these casual observations requires further clarification.

The clinical experience with streptokinase covers almost all types of thromboembolic diseases, certain areas having been studied more adequately than others. The observations on acute deep vein thrombosis indicate that about 50 to 60 percent of the treated vessels will show considerable angiographic clearing after streptokinase therapy, and the chance of resolution is much higher if the streptokinase is given within 96 hours of the clinical onset of symptoms. When evidence is provided that thrombus dissolution decreases the incidence of postphlebitic venous insufficiency, then thrombolytic therapy will become the immediate treatment of choice in the management of deep vein thrombosis.

In acute arterial thrombosis involving the lower limbs, satisfactory dissolution of thrombi can be anticipated in approximately half the treated patients; in embolic disease, the incidence of success is much higher. Surgery is still preferred to fibrinolytic therapy for aorto-iliac occlusion since the results of endarterectomy for this lesion are generally excellent, but streptokinase is considered more efficacious than surgery for the management of occlusions situated in the popliteal artery or more distally. In femoral artery thrombosis, streptokinase yields results comparable to those of surgery and currently is being used first unless there is evidence to suggest impending irreversible damage to the limb.

Opinions differ on the use of streptokinase for

TABLE II

Urokinase-Pulmonary Embolism Trial: Patient Characteristics

	Heparin (no. = 78)	Urokinase (no. = 82)	Total (no. = 160)
Class			
I-S	35	33	68
I-M	38	40	78
II-S	1	2	3
II-M	4	7	11
Sex			
Male	45	47	92
Female	33	35	68
Age (yr)			
<50	34	44	78
>50	43	36	79

Class I = patients without shock; Class II = patients with shock. M = massive embolism indicating occlusion of 2 or more lobar arteries with clot; S = submassive embolism involving at least 1 segmental artery.

the management of chronic arterial occlusions of the lower limb: some claim it is quite useful while others are less enthusiastic.

In acute pulmonary embolism 24 hours of streptokinase therapy has produced an effect similar to that recently reported for urokinase; significant lysis of pulmonary emboli has been achieved with a restoration of the hemodynamic abnormalities toward normal. As with urokinase, the effects are more striking with massive pulmonary embolism than with involvement of the smaller pulmonary arteries; this is not an unexpected finding since emboli in the main pulmonary artery or its major branches are more exposed to the action of the clot-dissolving agent. When one considers the high mortality associated with pulmonary embolectomy, particularly in the aged and in those with underlying heart disease, it is likely that thrombolytic therapy will become the initial therapy of choice for the management of most patients seriously ill with an acute massive pulmonary embolism.

Since a major goal has been to prove the usefulness of streptokinase in the management of acute myocardial infarction, a series of controlled multi-institutional trials have been undertaken abroad; to date, 3 have been concluded[14–16] and 1 is still underway.[17] In each, streptokinase has been infused continuously for a 24 hour period and as early as possible after hospitalization; however, there have been differences in design among the various trials. The first,[14] conducted in Germany, included 558 patients of whom 297 were treated with streptokinase and 261 with anticoagulant agents. The early, late and total mortality rates were considerably reduced in the group treated with streptokinase; the difference in the total mortality being significant at a P value of 0.05. Other conclusions drawn from this study were as follows: (1) Streptokinase therapy reduced mortality between the second and fortieth day after infarction from 22 to 14 percent; (2) no significant risk could be attributed to the use of streptokinase in acute myocardial infarction; (3) serial differences in the electrocardiogram between the 2 groups of patients suggested that streptokinase was beneficial in myocardial infarction; and (4) the higher incidence of rudimentary infarction in patients treated with streptokinase suggested that in a number of patients the early use of thrombolytic therapy was reducing the extent of cardiac muscle necrosis. Since the first trial did not employ appropriate randomization, corrections were made in a second German trial. The data from the latter[15] support the observations made in the first trial. Recently, a multicenter trial including hospitals in Germany, Holland, Austria and Belgium[16] has been concluded, and the results are being prepared for publication; preliminary analysis also indicates a reduction in mortality favoring streptokinase. Finally, in a trial[17] currently underway in Australia, the results from the first 127 patients also indicate a trend in favor of streptokinase. Thus, considerable evidence is beginning to accumulate that streptokinase therapy may play a useful role in the management of acute myocardial infarction.

Urokinase: The experience with urokinase is quite limited since this material has never been commercially available and its investigation is being restricted to carefully controlled trials in specific lesions. Urokinase is a plasminogen activator normally present in human urine; it is made by the kidneys presumably to keep the renal tubules and urinary tract free of fibrinous deposits. Its virtues lie in its nonantigenicity, nonpyrogenicity or other toxicity except bleeding, and its ability to induce a more reliable thrombolytic state with milder aberrations in the hemostatic mechanism than seen with streptokinase. After solution of the production problems, partially purified preparations of human urokinase free of toxic impurities were prepared by Sterling-Winthrop and Abbott Laboratories, and the clinical investigation of the agent sponsored by the National Heart and Lung Institute.

Following the acquisition of appropriate pharmacologic data in man[18] the initial evaluation of urokinase was undertaken in acute pulmonary embolism; most important in this choice was that pulmonary angiography, hemodynamic measurements and lung scanning were available to assess the effects of this agent on the embolism.

The recently concluded first phase of the multi-institutional Urokinase-Pulmonary Embolism Trial[19] has established the ability of a 12-hour intravenous infusion of urokinase to lyse pulmonary emboli, increase pulmonary capillary perfu-

sion and decrease the hemodynamic abnormalities associated with this disorder; the following figures taken from the presention of John Murray for the Urokinase-Pulmonary Embolism Trial Study Group at the 1970 annual meeting of the American Heart Association highlights the observations made:

Table II shows the patient distribution by drug, class, sex and age. The 160 patients who entered the trial were randomly allocated by class and institution for treatment with heparin or urokinase; 78 were treated with heparin and 82 with urokinase. The patients were classified by the presence or absence of shock. In class I are patients without shock; in class II are patients with shock; S and M refer to the angiographic classification of the size of the embolus—S or submassive embolism indicating involvement of at least 1 segmental artery and M or massive indicating occlusion of 2 or more lobar arteries with clot. There was an equal distribution between the 2 treatment groups by class and sex, but more young patients were in the group treated with urokinase.

Objective evaluation was dependent on hemodynamic, angiographic and lung scan data before and 24 hours after initiation of therapy. Figures 3 and 4 show hemodynamic data as percent change at 24 hours and the significance of the change between heparin and urokinase. The format is the same for all hemodynamic indexes. C.R. stands for critical ratio, which is the difference in mean change divided by the standard error. A critical ratio of 2.5 is of borderline significance, a critical ratio of 3.0 denotes full significance. Critical ratios, rather than the more conventional *P* values, were used throughout this study by our biometricians.

In the group treated with urokinase, there was a significant change of 9 mm Hg in arterial pO_2 at 24 hours representing a 14 percent increase; this contrasts with less than a 1 percent increase in the group treated with heparin. The critical ratio of 3.3 denotes full significance. Right atrial mean pressure (top panel, Fig. 4A), right ventricular systolic pressure (middle), and right ventricular end-diastolic pressure (bottom), all showed a 25 to 30 percent change toward normal

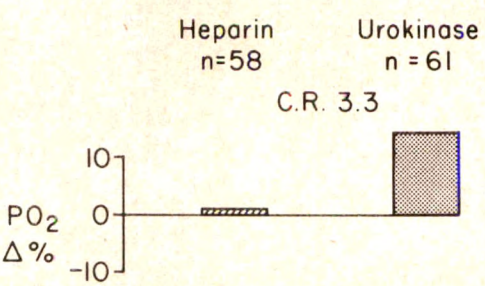

Figure 3. Urokinase-Pulmonary Embolism Trial: changes in pO_2 at 24 hours. C.R. = critical ratio.

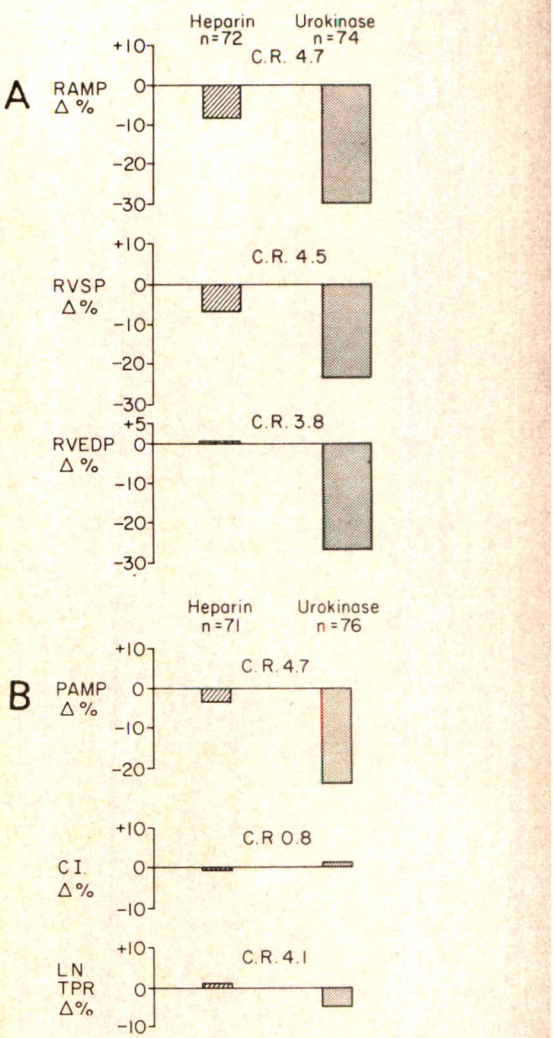

Figure 4. Urokinase-Pulmonary Embolism Trial: hemodynamic changes in 24 hours. CI = cardiac index; LN = natural logarithm; PAMP = pulmonary arterial mean pressure; RAMP = right atrial mean pressure; RVEDP = right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure; TPR = total pulmonary resistance.

in the urokinase-treated patients. The change in the heparin-treated group toward normal was less than 10 percent. The changes in all 3 indexes were highly significant in favor of urokinase. Note in Figure 4B that a 30 percent decrease occurred in pulmonary arterial mean pressure in the patients treated with urokinase as compared with a 4 percent decrease in those treated with heparin—a very significant difference. No significant change was observed in cardiac index, but the decrease in total pulmonary resistance, plotted in the lower part of Figure 4B as the natural logarithm, was highly significant in favor of urokinase.

The second objective parameter was the angiographic data, and Figure 5 shows the change in severity at 24 hours. On the ordinate is an improvement scale, 0 through 4, from no improvement to complete improvement. Neither class in the group treated with heparin showed significant

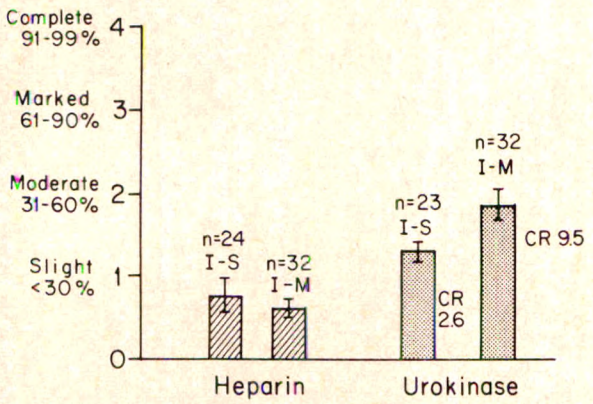

Figure 5. Urokinase-Pulmonary Embolism Trial: improvement in severity of pulmonary angiographic changes at 24 hours.

improvement. In contrasting Class I-S patients in the 2 groups, the improvement with urokinase was only borderline significant. However, with Class I-M patients there was a striking difference in improvement of over a grade and a half favoring treatment with urokinase; this is highly significant with a critical ratio of 9.5.

The third objective parameter was the lung scan data, shown in Figure 6 as percent resolution from the base line for patients with massive embolism. The data were collected on days 1, 2, 3, 5, 7 and 14 after treatment, but it was anticipated that the effect of urokinase would be restricted to the first day. As can be seen, a highly significant improvement in resolution occurred at 24 hours favoring urokinase. However, when the patients with submassive embolism were also included, the effects were less striking and only borderline significance was achieved.

The major complication in the trial was bleeding and the observations relative to this complication are summarized in Table III. Six of 78 patients treated with heparin had bleeding problems asso-

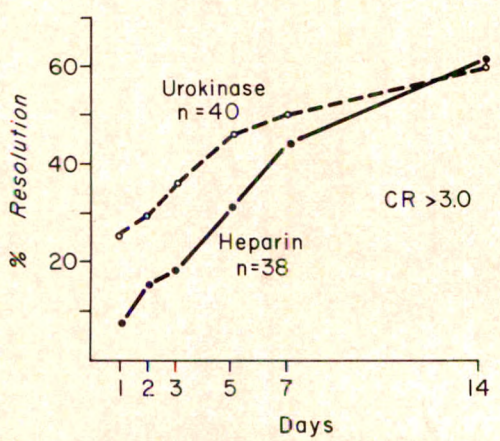

Figure 6. Urokinase-Pulmonary Embolism Trial: improvement in lung scan data (percent change from base line in patients in class I–M [patients without shock and massive embolism]).

TABLE III

Urokinase-Pulmonary Embolism Trial: Bleeding Complications

Type	Heparin (no. = 78)	Urokinase (no. = 82)
Cutdown site	6	20
Spontaneous	15	16
Total	21 (27%)	36 (44%)

ciated with the cutdown or arterial puncture sites. Spontaneous bleeding occurred with equal frequency. The increased frequency of bleeding among the patients treated with urokinase is a reflection of the well known tendency of patients on thrombolytic therapy to bleed excessively from venous cutdowns and arterial punctures during therapy. Although of real concern, this risk was anticipated since a number of invasive procedures had to be performed in order to obtain the required information.

Phase II of Urokinase-Pulmonary Embolism Trial: The ability of urokinase to dissolve clots and to restore toward normal the hemodynamic aberrations in acute pulmonary embolism has important therapeutic implications particularly for patients with massive embolism and shock. However, the trial evaluated only 1 urokinase treatment regimen, that is, a 12-hour infusion. Accordingly, although thrombus resolution was unequivocal, it was not dramatic in terms of lysing the entire pulmonary occlusion or of completely resolving the hemodynamic abnormalities. On the basis of experience, it can be predicted that a longer treatment period will more closely approach the goal of a complete medical thrombectomy without further increasing the risk of hemorrhage; certainly, if this can be accomplished it would be a much more useful regimen for the therapy of patients critically ill with acute pulmonary embolism as well as for the management of other thromboembolic lesions. For this reason, the second phase of the Urokinase-Pulmonary Embolism Trial is underway; patients are now being randomly divided into 3 groups: those receiving 12 hours of urokinase as before; those receiving a 24 hour infusion of urokinase and those receiving 24 hours of streptokinase therapy. Besides yielding information as to the effects of a longer urokinase infusion, this new phase will provide the first comparison between the thrombolytic effects and hazards of the 2 major promising thrombolytic agents when used according to current dosage schedules. Phase II was initiated in the fall of 1970, and over 30 patients have been studied in the first 4 months. It is likely that this phase will be concluded relatively quickly and yield information most helpful for the planning of a major trial aimed at estab-

lishing the benefit of thrombolytic therapy in acute myocardial infarction.

Implications for management of acute myocardial infarction: Since the long-term goal of the National Heart and Lung Institute, in its active encouragement of the development of thrombolytic agents, always has been to evaluate their possible beneficial effects in the treatment of acute myocardial infarction, it is gratifying to note that the time for the institution of such a trial has finally arrived. One may anticipate that it will involve both an evaluation of streptokinase and urokinase, for each has its advantages and disadvantages. If the results of such a trial indicate a highly significant decrease in morbidity and mortality, then a major new advance will have been provided for the management of acute myocardial infarction, and will justify all the time, effort and support which has gone into this area of investigation. Personally, I am optimistic that this will be achieved.

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Mitral Valvular Abnormalities Associated with Supravalvular Aortic Stenosis

Observations in 3 Cases

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In 3 of 5 specimens of heart from patients with supravalvular aortic stenosis, lesions of the mitral valve were observed. In the youngest patient, an infant, the changes consisted of collagenous thickening of leaflets and mild degrees of protrusion of segments of the leaflets toward the left atrium (hooding). In the 2 older subjects, aged 7 and 38 years, respectively, the processes of hooding and valvular thickening were pronounced. In addition, each of the latter 2 patients had endocardial fibrous lesions of the left ventricular endocardium related to thick chordae attaching to the posterior leaflets. In the oldest subject, chordae were adherent to the related left ventricular endocardium.

The lesions of the mural endocardium and of the chordae are considered to result from friction incident to the underlying valvular hooding. Since the material was limited in amount, it is uncertain whether the mitral valvular changes represent a coincidental or true association with supravalvular aortic stenosis.

Supravalvular aortic stenosis is recognized as an obstructive congenital deformity of the ascending aorta which originates just distal to the level of the coronary arterial origins. Three types have been described: the hourglass, the hypoplastic and the membranous, each term identifying the gross characteristic of the lesion causing the aortic obstruction.[1]

Noncardiovascular conditions commonly associated with supravalvular aortic stenosis are mental retardation, facial anomalies[2,3] and hypercalcemia.[4,5]

Supravalvular aortic stenosis may be accompanied by other pathologic conditions, both cardiovascular and noncardiovascular. Commonly associated cardiovascular lesions are (1) adhesion of the aortic semilunar cusps to the obstructive deformity in the ascending aorta, (2) structural abnormalities of the coronary arteries, a feature related to the presence of high pressure within these vessels, (3) stenosis of branches of the aortic arch, and (4) pulmonary arterial stenosis involving either the main arteries or the peripheral ones.[1,6]

This report describes 3 cases of abnormalities of the mitral valve found among 5 specimens of heart with supravalvular aortic stenosis at our disposal. The uncommon recognition of mitral valvular lesions with supravalvular aortic stenosis is indicated by the fact that, in a survey of 175 cases of supravalvular aortic stenosis reported in the English language, only 2 cases were found

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Figure 1. Case 1. Opened aortic valve and ascending aorta. The aortic cusps, 3 in number, are thickened. The aortic wall shows major thickening.

in which pathologic examination revealed abnormalities of the mitral valve.[7,8] In addition, a few cases have been described in which mitral insufficiency was recognized clinically.[9–12]

Description of Cases

Case 1: A baby girl was hospitalized shortly after birth with congestive heart failure and cyanosis. The electrocardiogram showed right atrial dilatation and right ventricular hypertrophy. Thoracic roentgenograms revealed decreased to normal pulmonary vascularity. A grade 3/6 harsh systolic murmur of the ejection type was heard over the left lower sternal border. Given supportive treatment, the infant failed to thrive and died of pneumonia at the age of 4 months.

At necropsy, the ascending aorta, aortic arch and pulmonary trunk were uncommonly thick-walled (Fig. 1). The calibers of the aorta and pulmonary trunk were near normal in diameter, but each of these vessels histologically showed the medial mosaic pattern classically seen in supravalvular aortic stenosis.[8,13] The 3 cusps of the aortic valve were thickened and opaque.

The mitral valve was of particular interest. Its leaflets were uniformly thickened to moderate degree and showed a minimal degree of protrusion toward the left atrium, a process which we have termed "hooding" (Fig. 2a). The papillary muscles and chordae were normal. Histologic study of the mitral leaflets showed the thickening to be caused by an increase in collagenous fibrous tissue with a tendency for the collagenous bundles to be surrounded by a loose matrix (Fig. 2b).

There were no other intracardiac abnormalities. The left atrium was not enlarged.

Case 2: In a boy, aged 5 years, a cardiac murmur was discovered at age 13 months, and a diagnosis of supravalvular aortic stenosis was made. Surgical correction was attempted by inserting a Teflon® patch in the most narrow aortic segment, just above the aortic valve. The general condition of the child improved. However, at age 7 years, a mycotic aneurysm at the junction of the aortic arch and descending aorta was discovered. The child died 17 days after resection of the aortic aneurysm.

Necropsy revealed supravalvular aortic stenosis of the hypoplastic type with continuation of the hypoplastic process to involve the entire thoracic aorta and the origins of the branches of the aortic arch. The wall of the pulmonary trunk was thick-walled without luminal narrowing. The Teflon patch inserted in the ascending aorta 2 years previously was found encased by fibrous tissue and covered by a neo-intima (Fig. 3).

Several abnormalities of the mitral valve were noted. The leaflets were uniformly thickened, gray and opaque. Each showed a marked degree of "hooding" (Fig. 4a). The chordae shared with the leaflets the process of thickening. The papillary muscles were normal. In relation to chordae attaching to the posterior

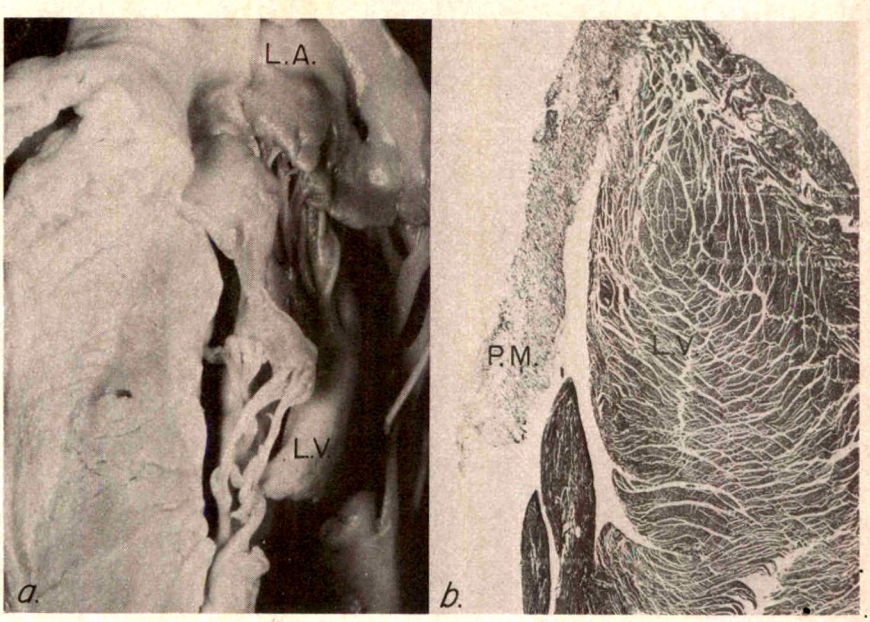

Figure 2. Case 1. **a,** portion of the left atrium (L.A.), left ventricle (L.V.) and the mitral valve. The mitral valve leaflets are thickened and show mild degrees of protrusion toward the left atrium (hooding). **b,** photomicrograph of posterior mitral leaflet (P.M.) and related left ventricular wall (L.V.). The mitral leaflet is thickened by collagenous tissue lying in a loose matrix. (Elastic tissue stain ×7.3, reduced by 21 percent.)

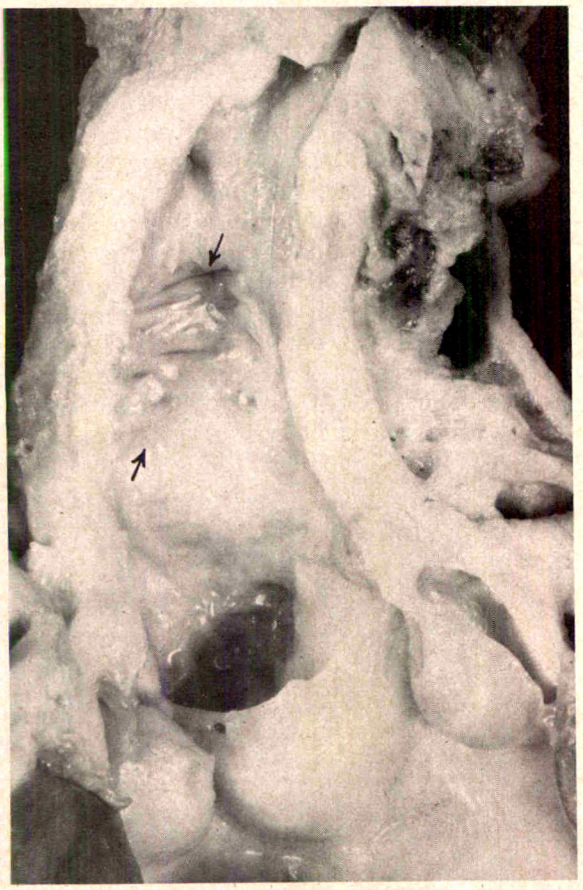

Figure 3. Case 2. The opened aortic valve and ascending aorta. In the aorta, the rough area (between arrows) represents the site of previous surgical placement of a teflon patch to widen the aorta. The aortic wall is uniformly thickened. The picture is that of hypoplastic supravalvular aortic stenosis.

mitral leaflet, the left ventricular endocardium showed linear thickenings (Fig. 4a). Histologically, the mitral valvular leaflets were thickened by fibrous tissue. Chordae were thickened by a surface deposit of collagen. The left ventricular endocardial thickening was caused by collagenous deposit (Fig. 4b).

No other cardiac abnormalities were noted and the left atrium was not enlarged.

Case 3: A 38 year old woman had been hospitalized since childhood because of mental retardation. Clinically, supravalvular aortic stenosis was recognized. Death was sudden and unexpected.

Pathologic examination showed stenosis of the ascending aorta just distal to the semilunar valves, the deformity being classic for the hourglass type of supravalvular aortic stenosis (Fig. 5a). The commissural aspects of the aortic valvular cusps were intimately related to the deformity of the aorta.

The mitral valve was grossly abnormal in several respects. Prominent thickening and hood-like protrusion toward the left atrium of both leaflets were observed, the "hooding" being more marked in the posterior leaflet (Fig. 5, b and c). At the center of the greatest degree of hood-like deformity in the posterior leaflet was a perforation measuring about 4 mm in diameter. The edges of the perforation were smooth. No vegetations were present. On the septal wall of the left atrium, opposite the valvular perforation, was a series of jet lesions. The left atrial chamber was enlarged.

Thickening of the leaflets was diffuse but with accentuation of the process in the center of the anterior leaflet opposite the site of perforation in the posterior leaflet. Gray, fibrous thickening of chordae was striking, particularly of the posteromedial group. Isolated chordae of this group were fused to fibrous tissue which thickened the mural endocardium of the related left ventricular wall (Fig. 5c).

Histologic examination of the mitral valve revealed several features including (1) major collagenous thickening of the tissue of the leaflet, (2) healing of the edges of the perforation in the posterior leaflet without identifiable vegetations or leukocytic infiltration, although a few small blood vessels were present in the thickened leaflet, (3) encasement of chordae by fibrous tissue, (4) thickening of that portion of the left ventricular endocardium which was related to the chordae of the posterior mitral leaflet, and (5) adhesion of chordae to left ventricular endocardium (Fig. 5d).

Comment

This report describes abnormalities of the mitral valve in 3 among 5 cases of supravalvular aortic stenosis. In 2 of the 3 cases described, the aortic lesions were classic for supravalvular aortic stenosis. In Case 1, although the aortic lumen did not appear to be narrowed, the walls of the aorta and pulmonary trunk were abnormally thick and presented a mosaic structure like that seen in classic examples of supravalvular aortic stenosis.[8,13] We believe that this case exhibits inherent characteristics sufficient for categorization as supravalvular aortic stenosis.

The relatively common occurrence of mitral valvular lesions in our limited material is contrary to the paucity of reference to such an association in pathologic and clinical descriptions. We are aware of only 2 cases reported in the English language which describe structural mitral valvular changes in patients studied at necropsy with supravalvular aortic stenosis.

In 1959 Sissman and associates[7] reported the case of a 70 year old woman (their Case 4) with a membranous type of supravalvular aortic stenosis in which the mitral valve was described as "somewhat thickened, but otherwise unremarkable." Neufeld et al.[8] described a 2 year old boy with the hypoplastic type of supravalvular aortic stenosis in which there was fibrous thickening of the posteromedial commissure of the mitral valve and related parts of the anterior and posterior leaflets.

In addition, the literature contains reference to a few cases of supravalvular aortic stenosis in which mitral valvular abnormalities might have been present. Five cases of supravalvular aortic stenosis with mitral insufficiency have been described clinically,[9–12] and an additional case has been reported in which an enlarged left atrium was present.[14]

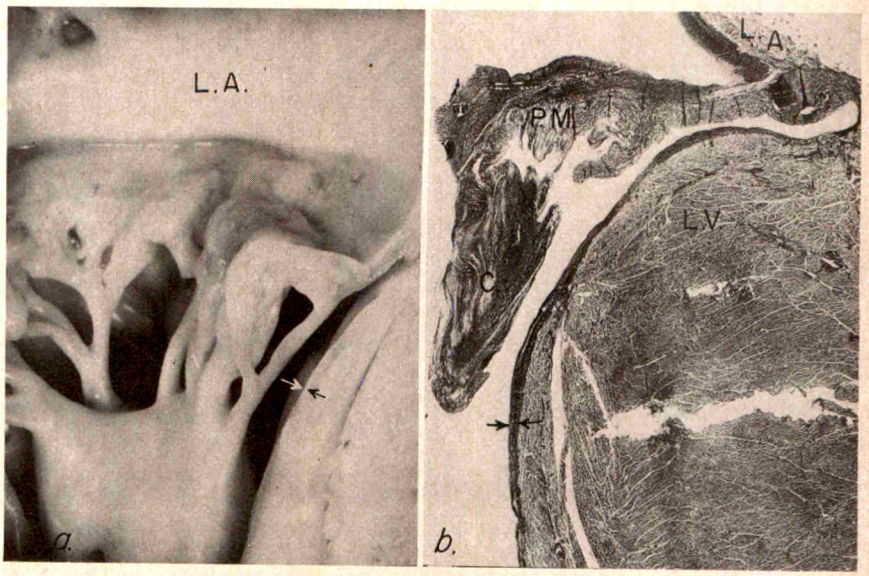

Figure 4. Case 2. **a,** closeup view of a portion of left atrium (L.A.) and region of posteromedial commissure of mitral valve. The valvular leaflets and chordae are thickened. Minimal thickening of left ventricular endocardium (between arrows) related to chordae attaching to the posterior mitral leaflet. **b,** photomicrograph of section through wall of left atrium (L.A.), left ventricle (L.V.) and posterior mitral leaflet (P.M.). The leaflet is thickened. Chordae (C.) attaching to the leaflet show fibrous thickening. The mural endocardium of the left ventricle is thickened with collagenous tissue (**between arrows**). (Elastic tissue stain ×5, reduced by 25 percent.)

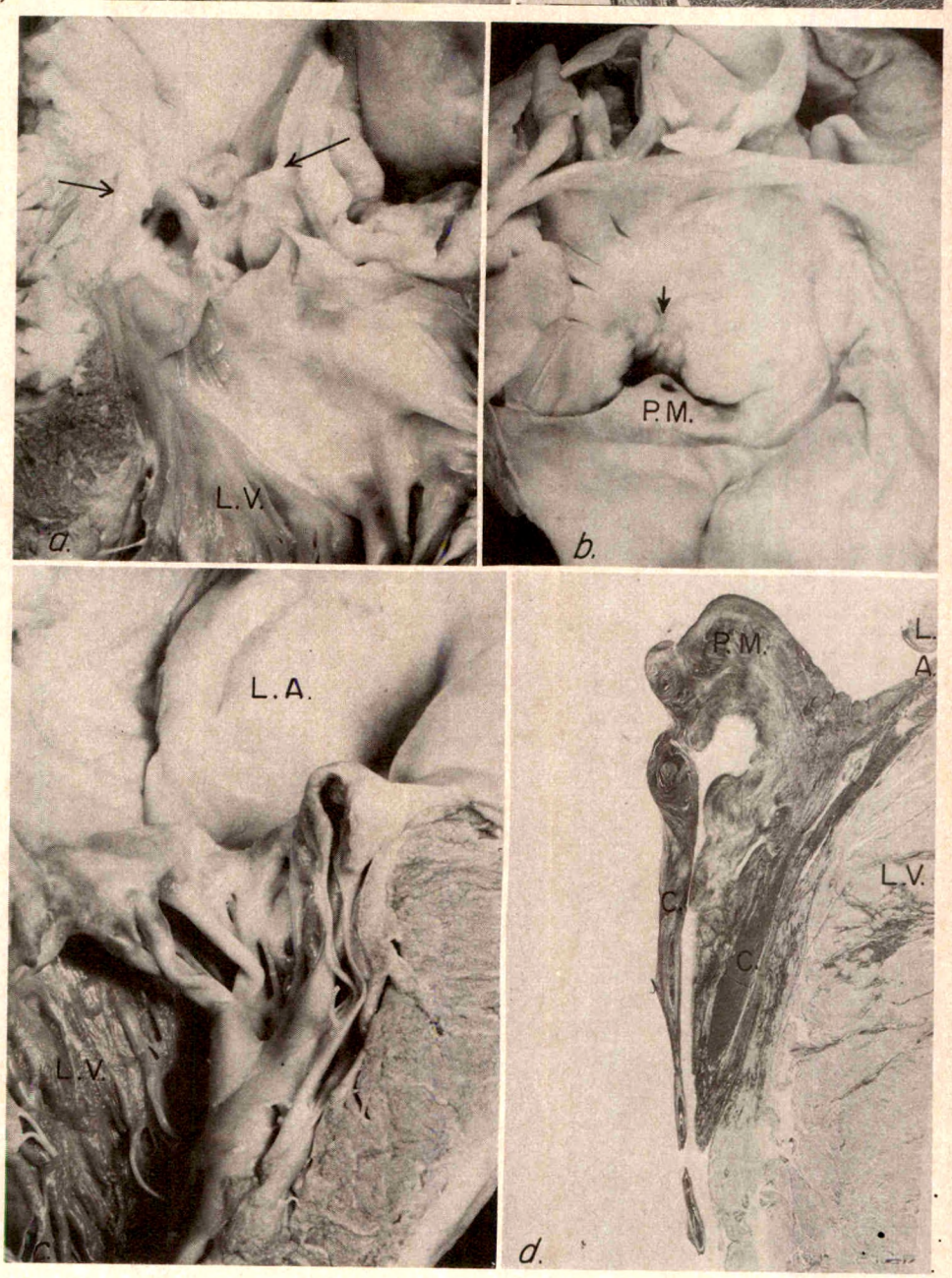

Figure 5. Case 3. **a,** opened base of left ventricle (L.V.) and ascending aorta. Above the aortic valve, the aortic wall shows major thickening with obstruction by protrusion of tissue from aortic wall into the lumen (**between arrows**). The picture is characteristic of the hour glass type of supravalvular aortic stenosis. **b,** unopened mitral valve viewed from above. In the posterior mitral leaflet (P.M.) is a small perforation. Opposite this, the anterior leaflet shows a focus of considerable fibrous thickening (**arrow**). There is focal hooding of each leaflet. **c,** opened left atrium (L.A.), left ventricle (L.V.) and mitral valve. The posterior leaflet of the mitral valve, which has been sectioned, shows major hooding. Near the commissure, chordae of the posterior mitral leaflet show adhesion to the thickened left ventricular endocardium. **d,** photomicrograph through wall of the left atrium (L.A.), left ventricle (L.V.) and posterior mitral leaflet (P.M.). The leaflet shows hooding and thickening with collagen. The chordae (C.) are encased by collagen. One is adherent to the thickened mural endocardium of the left ventricle. (Elastic tissue stain ×3, reduced by 16 percent.)

The nature of the mitral valvular lesions brings up for consideration the possibility of a coincidental association with some other syndrome such as gargoylism or Marfan's syndrome (arachnodactyly). The absence of specific storage cells on histologic examination is considered sufficient reason to disregard the similarity in appearance as having any bearing on the origin of the lesions in our cases.[15]

The presence of hooding of the mitral valvular leaflets calls to mind Marfan's syndrome (arachnodactyly), since supravalvular aortic stenosis has been described in patients with arachnodactyly.[13,16,17] There are several features which are against accepting the valvular hooding as part of arachnodactyly. These include (1) absence of the characteristic body build of the patients, (2) absence of cystic medial necrosis of the aorta, and (3) the presence of coarse, rather than delicate, valvular tissue.

In a variety of cases in which mitral valvular "hooding" was common, Salazar and Edwards[18] described friction lesions of the left ventricular endocardium in relation to chordae of the posterior mitral leaflet. These changes consisted of linear endocardial thickening and fusion of the mural endocardium with the related chordae. In our 3 cases of supravalvular aortic stenosis, the spectrum of changes described by Salazar and Edwards are portrayed. We therefore believe that the changes in the mural endocardium are secondary to the valvular hooding.

In Case 3, wherein a perforation in the posterior leaflet was associated with focal thickening of the anterior leaflet, an element of bacterial endocarditis, now healed, cannot be excluded as a partial basis of adhesion of chordae to the left ventricular endocardium.

It is impossible from the material at hand to evaluate the functional consequences of the mitral valvular changes observed. In Cases 1 and 2 the left atrium was of normal size, whereas in Case 3 the left atrium was enlarged. This suggests that mitral insufficiency, in addition to that occurring through the perforation in the posterior leaflet, might have been present.

Reports associating mitral valvular lesions with supravalvular aortic stenosis are uncommon. Therefore, whether the association in our 3 cases is mere coincidence or a true association remains an unanswered question. Study of future cases with an awareness of the possibility of association of the 2 conditions will perhaps serve better to answer the question than is now possible.

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Malfunction of Mitral Ball Valve Prosthesis Due to Thrombus

Report of 2 Cases with Notes on Early Clinical Diagnosis

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Two cases are reported in which malfunction of a mitral ball valve prosthesis (Cutter-Smeloff type) was diagnosed by auscultation, phonocardiography (demonstrating delay in the valve opening sound) and echocardiography (showing delayed opening of ball as well as delayed cage motion). In both patients prosthetic dysfunction was caused by the ingrowth of fibrin clot, preventing proper excursion of the ball. In 1 patient, sufficient valve malfunction developed to result in cardiac failure; in the second patient, who remained well, the diagnosis of valve malfunction was made on routine follow-up examination. Both underwent successful reoperation.

Our cases demonstrate that delayed opening of a malfunctioning prosthetic mitral valve is not limited to ball variance. We recommend frequent phonocardiographic and echocardiographic examination for patients with a ball valve prosthesis in the mitral position, and suggest that early surgical intervention be considered in those with abnormal function of the prosthesis.

Of the late complications resulting from the use of prosthetic ball valves, ball variance has attracted a great deal of attention, especially in patients with a Starr-Edwards prosthesis in the aortic position.[1–3] In contrast, there are only a few reported cases of ball variance in mitral valve prostheses,[4–7] and all of these have occurred with use of the Cutter-Smeloff valve. This communication records 2 cases of malfunction of the Cutter-Smeloff prosthesis caused by overgrowth of the valve with fibrin clot. In both cases, the ball was normal.

Case Reports

Case 1: A 31 year old housewife had acute rheumatic fever at age 8 years. Ten years later, during her first pregnancy, she had signs and symptoms of cardiac failure and was found to have mitral regurgitation. After childbirth, repeated attacks of atrial fibrillation occurred, associated with congestive failure. Mitral valvuloplasty was performed at age 20 years in 1959. Despite the persistence of an apical pansystolic murmur, cardiac size diminished considerably, and the patient remained asymptomatic and had normal sinus rhythm. Two years after operation (1961), a recurrence of paroxysmal atrial fibrillation was noted, and over the next 4 years her condition deteriorated to her preoperative status. At reoperation in 1965, the mitral valve was found to be grossly incompetent due to fibrosis and retraction of the leaflets; it was replaced with a Cutter-Smeloff prosthesis. Three years later, despite remarkable clinical improvement and adequate anticoagulation, the patient had an episode of dizziness and transient numbness on one side of her body; a diagnosis of cerebral embolus was made. Five years after valve replacement (1970), cardiac failure returned and persisted despite vigorous medical therapy.

From the Heart Research Institute, the Institute of Medical Sciences, and the Cardiopulmonary Unit, Presbyterian Hospital, Pacific Medical Center, San Francisco, Calif. This study was supported by Grants HE-05598 and HE-06311, National Institute of Health, U. S. Public Health Service, Bethesda, Md. Manuscript received September 4, 1970, accepted November 11, 1970.

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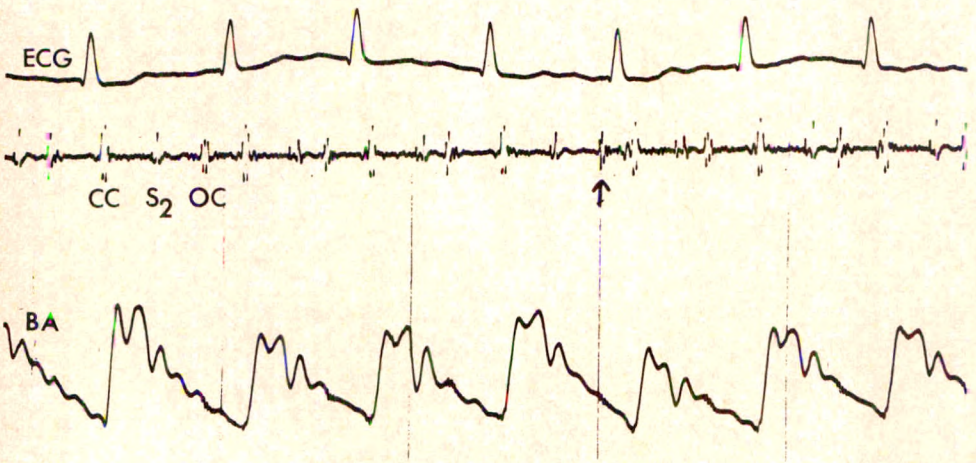

Figure 1. Case 1. Simultaneous phonocardiogram and intraarterial pressure tracing. Careful measurement of the intervals between the second heart sound (S2) and opening click (OC) and preceding R–R cycles reveals occasional inappropriate delay in opening of the mitral valve prosthesis (**arrow**). After such delay, brachial arterial (BA) pressure is decreased. CC = closing click.

Pertinent physical findings on admission were as follows: normal blood pressure, atrial fibrillation and prominent jugular venous pulsations in the sitting position indicating increased right atrial pressure and tricuspid regurgitation. The lungs were clear. The apical impulse was not displaced, but a left parasternal heave was present. A grade 3/6 pansystolic murmur was heard medial to the apex. The clicks of the prosthetic valve were clearly audible, but the opening click was thought to vary in its relation to the second heart sound, regardless of the length of the preceding R–R interval; in some cycles it was entirely inaudible. There was moderate hepatomegaly but no peripheral edema. The electrocardiogram revealed atrial fibrillation and digitalis effect on the S–T segments. A chest roentgenogram showed marked left atrial and right ventricular enlargement and pulmonary vascular congestion.

Phonocardiographic examination (Fig. 1) revealed intervals of various lengths between the second heart sound and opening click which were not always related to the length of the preceding R–R intervals. Echocardiography (Fig. 2) demonstrated delay in opening of the prosthetic ball as well as delayed motion of the entire cage. Cardiac catheterization (Table I) showed abnormal hemodynamic values and a gradient across the mitral valve. Cineangiography demonstrated a filling defect within the mitral prosthesis (Fig. 3).

At a third operation, the rim of the valve was found to be the site of a large ingrowth of thrombus. The operative report stated that "the fibrin buildup effectively prevents the ball from moving more than approximately 2 millimeters." Because of the improper seating of the ball in the closed position, mild mitral regurgitation was present. A Starr-Edwards prosthesis was placed, and the patient made an uneventful recovery, during which all signs of cardiac failure disappeared.

Case 2: A 51 year old man had acute rheumatic fever at age 10 years. He was known to have a heart murmur since that time, but remained in good health until age 47 when progressive effort dyspnea developed. He was found to have atrial fibrillation, but conversion to sinus rhythm with quinidine resulted in only slight clinical improvement. Since he found it difficult to pursue his occupation, he was referred for surgical evaluation in 1966. Physical examination at the time revealed normal blood pressure and regular sinus rhythm. The apical impulse was normally placed, but a slight left parasternal heave was present. The first heart sound was normal in intensity and the second sound

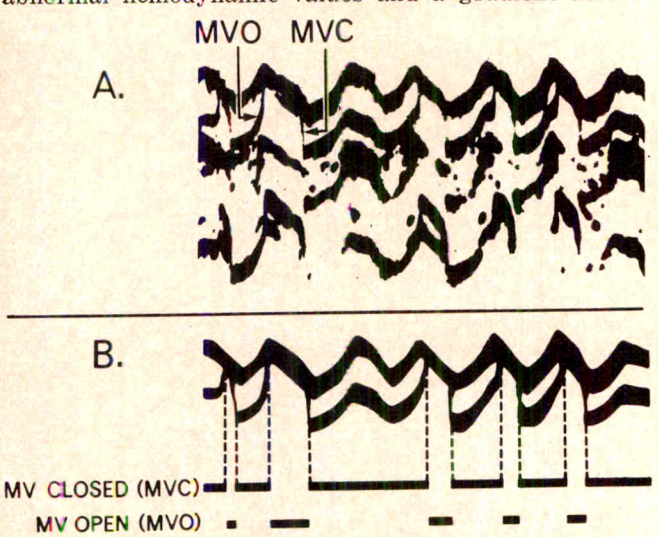

Figure 2. Case 1. Echocardiogram (**A**) with diagram of events (**B**). The electrocardiogram is unfortunately not seen in this Polaroid reproduction. Mitral valve opening (MVO) is periodically delayed. MVC = mitral valve closure.

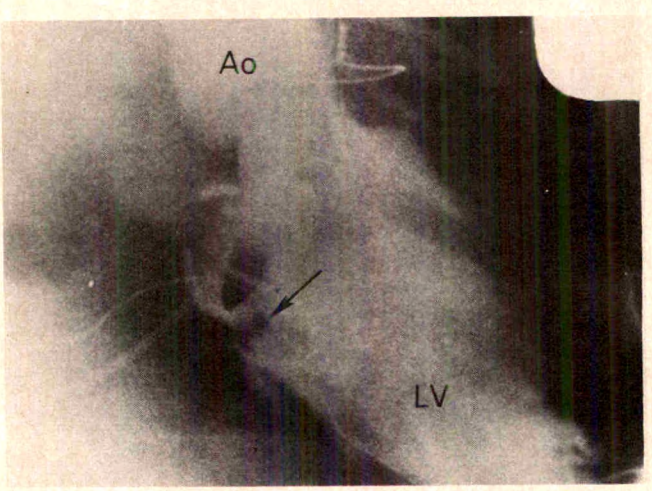

Figure 3. Case 1. Frame from cineangiogram. There is a filling defect in the prosthesis (**arrow**), representing ingrowth of fibrin clot. Ao = aorta; LV = left ventricle.

TABLE I

Serial Catheterization Studies in Cases 1 and 2

	Case 1					Case 2	
	1961	1963	1965	1967	1970	1966*	1970†
Pressures (mm Hg)							
Right ventricular	40/13	32/10	41/14	36/13	69/23	70/6	44/11
PAM	26	24	34	19	49	53	26
PAW							
Rest	19	21, v = 28	22, v = 32	27, v = 34	32, v = 38	33	15
Exercise	...	34	32	27	...	38	29
Cardiac index (liters/min per m²)							
Rest	2.2	1.6	2.1	3.2	2.3	2.9	3.3
Exercise	...	2.5	2.9	5.5	...	3.7	...
Mitral gradient (mm Hg)	14	17	18	17	17	23	9

* Preoperative values; † 4 years after valve replacement.

split normally; no opening snap was heard. There was a grade 2/6 pansystolic apical murmur and a loud, long diastolic rumble with presystolic accentuation. No clinical signs of cardiac failure were present. The electrocardiogram showed a left-sided conduction defect, and a chest roentgenogram revealed moderate cardiac enlargement involving primarily the left atrium and right heart chambers. Pulmonary vascular congestion was present as was heavy calcification in the region of the mitral valve. Cardiac catheterization (Table I) demonstrated hemodynamic abnormalities due to mitral valve disease with predominant stenosis. During open heart surgery in 1966, a heavily calcified deformed mitral valve was excised and replaced by a Cutter-Smeloff ball valve prosthesis. The patient made a satisfactory recovery and regained normal effort tolerance. He continued to receive anticoagulant medication, and was not seen again until 4 years later in 1970 when he presented for routine checkup. In the interim he had been able to pursue normal activities, including tennis-playing.

Physical examination at this time revealed regular sinus rhythm and normal blood pressure. No murmurs were heard. The closing click of the mitral prosthesis was normal, but the opening click sounded delayed at times, resulting in various lengths of the interval between the second heart sound and opening click. Phonocardiographic evaluation (Fig. 4) confirmed the delay in opening of the valve, and also showed inequalities in the carotid pulse tracing, recordings of lower amplitude being related to longer lengths of time that the mitral valve remained closed in the preceding beat. Echocardiography (Fig. 5) demonstrated the delay in opening of the prosthetic ball, which was associated with delayed motion of the cage. Cardiac catheterization (Table I) showed normal hemodynamic data at rest, with abnormal elevation of the pulmonary wedge pressure on exercise. Cineangiography did not demonstrate abnormality of motion of the ball valve.

Despite the normal clinical status of the patient, exploration of the valve was recommended. At operation, the ball was found to be fixed within the valve ring in the closed position (Fig. 6). The operative report stated that "it was easily displaced by the surgeon's finger, however, and apparently had been sticking intermittently. Tissue had grown over portions of the seat of the valve and also completely around one of the struts." The valve was excised and replaced with an autologous fascia lata valve, and the patient made an uneventful recovery.

Discussion

Malfunction of prosthetic ball valves has become an important problem in the long-term follow-up study of patients with artificial valves. Ball variance in aortic prostheses is well known, and its early recognition by auscultation, phonocardiography as well as the more recently described technique of sound spectrography has been re-

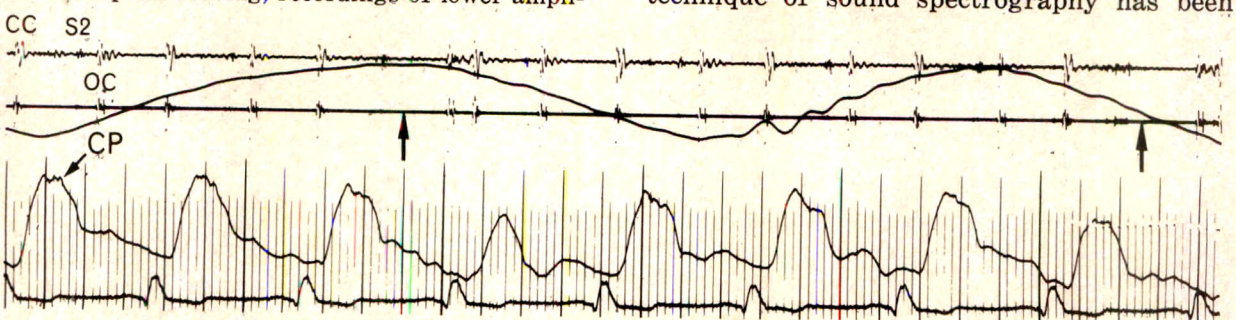

Figure 4. Case 2. Simultaneous phonocardiogram and carotid pulse tracing. **Arrows** indicate the expected time of opening of the prosthetic valve; the opening click (OC) is delayed in both cycles and is followed by a carotid pulse tracing (CP) with diminished amplitude. CC = closing click.

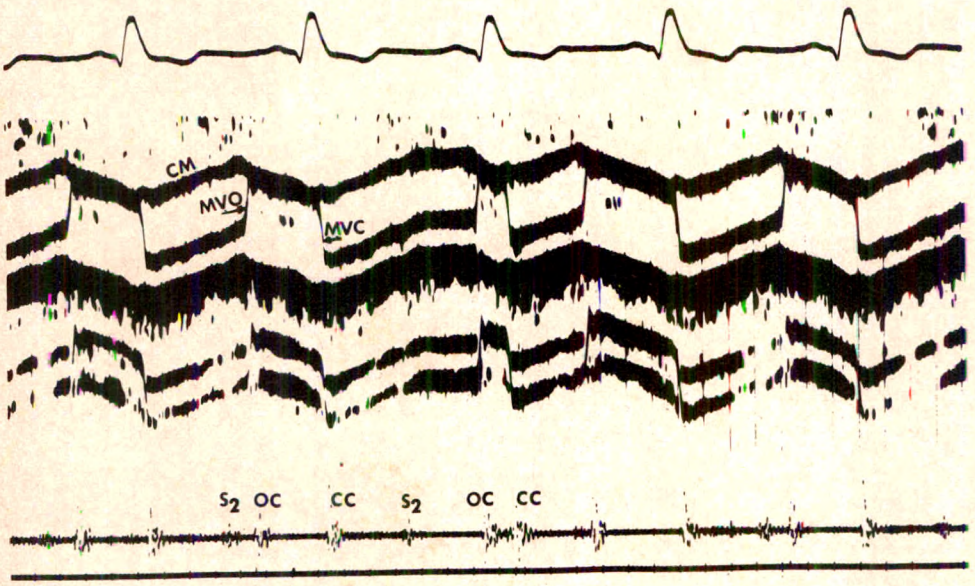

Figure 5. Case 2. Simultaneous echocardiogram and phonocardiogram (recorded on an Electronics for Medicine DR-8 recorder). Mitral valve opening (MVO) is delayed at times; the delay in valve opening is associated with abnormal motion of the cage (CM). MVC = mitral valve closure.

peatedly emphasized.[1-3] Such degenerative changes in the ball of the Starr-Edwards mitral prosthesis appear to be rare, and no detailed case reports are available. However, the Cutter-Smeloff prosthesis has recently been found to be associated with ball variance.[4-7] An early sign of such a complication is a consistent or intermittent delay in the opening sound of the mitral valve.

Thrombotic complications following insertion of valve prostheses are common[8,9] and have led to major efforts to modify the structure and materials of the prosthesis and to develop various types of tissue valves. Anticoagulation has not been shown to answer adequately the problem of thrombosis.

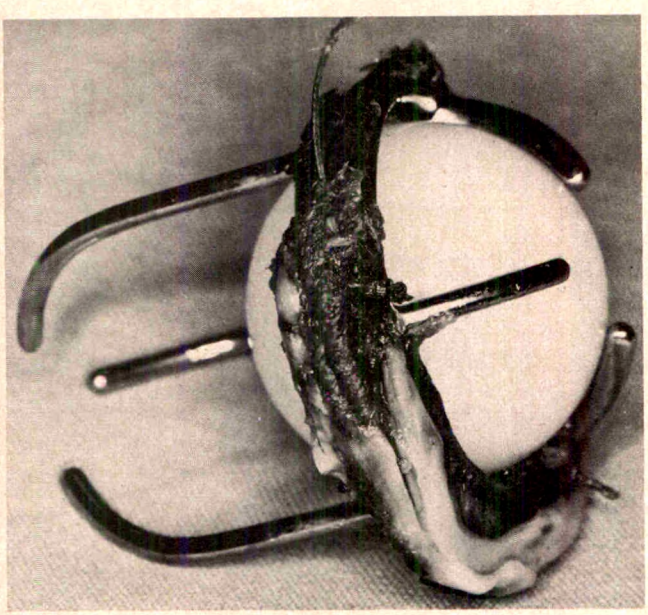

Figure 6. Case 2. Appearance of the prosthetic valve at surgery. Most of the fibrin clot was removed to facilitate excision. The ball is seen to be stuck in the closed position, and fibrin fragments are impinging on the metal struts.

Complications of this sort in mitral ball valve prostheses account not only for serious embolic events[7] and congestive heart failure[8] but also for late deaths.[10] The diagnosis of thrombosis of a Starr-Edwards mitral valve has been suspected clinically by the complete disappearance of the opening click of the prosthesis.[8]

The 2 cases reported herein are noteworthy for several reasons. First, the malfunction of the Cutter-Smeloff prosthesis was manifested by a delayed opening click, a finding heretofore considered characteristic of ball variance; in both our cases the ball appeared to be entirely normal. Second, it is shown that it is possible to diagnose the presence of valve malfunction by auscultation and phonocardiography even before clinical symptoms appear. Third, we believe that these are the first reports of the use of the echocardiogram as an aid in the diagnosis of prosthetic valve dysfunction. This technique clearly illustrates the motions of both ball and cage and, as expected, if the opening of the ball occurs late, motion of the entire prosthetic apparatus will also be delayed.

Clinical implications: On the basis of our experience it seems justified to recommend frequent reexamination including phonocardiographic and, where possible, echocardiographic evaluation of all patients with a mitral ball-valve prosthesis. Whereas the crucial feature in the diagnosis of malfunction of an aortic prosthesis is the ratio of opening and closing click amplitudes, early recognition of mitral valve malfunction depends on careful measurement over long periods of time of the intervals between the second heart sound and opening click. Although none of the diagnostic techniques described aid in distinguishing mitral ball variance from abnormal ball motion due to limitation by clot, the morbidity and mortality associated with such prosthetic dysfunction demands early surgical intervention.

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Extralobar Pulmonary Sequestration

Presentation as an Arteriovenous Aneurysm with Cardiac Failure in Infancy

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A case of extralobar sequestration precipitating cardiac failure in infancy is presented. The pre- and postoperative hemodynamic and angiocardiographic findings are reported. The literature is briefly reviewed. This case is possibly the first such case fully investigated and successfully treated in early infancy. It illustrates another cause of high output cardiac failure in this age group.

Pulmonary sequestration has been recognized with increasing frequency as an underlying cause of recurrent chest infections in children and adults since Pryce[1] published his series of 7 cases found in over 280 pulmonary resections. With the development of angiocardiographic techniques the hemodynamic effects of pulmonary sequestration have been described.[2,3] The diagnosis of pulmonary sequestration is rarely made before infection or other complications have occurred, and these are unusual in the neonatal period.

The hemodynamic, angiocardiographic and operative findings of extralobar pulmonary sequestration presenting with cardiac failure in the neonatal period are described in this report.

Case Report

A white male infant was born after a full-term normal pregnancy and delivery. Over the next few hours rib retraction developed. There was no cyanosis. The infant's condition failed to improve with symptomatic treatment. At age 18 hours he was admitted to the Children's Hospital. On admission, physical examination revealed a well-developed infant weighing 3.76 kg. He was slightly icteric but not cyanotic. There was evidence of mild respiratory distress. Air entry was diminished at the left base. Pulse rate was 152/min. No murmurs were audible.

A chest roentgenogram shortly after birth showed displacement of the heart to the right with opacities in the right upper zone and an opacity in the left lower zone behind the heart with a convex lateral margin. Later films showed resolution of the right upper zone lesion with the mediastinum returning to the midline, but persistence of the opacity at the left base. These appearances were thought to be consistent with a resolved atelectasis of the right upper pulmonary lobe and possible sequestration of the left lower lobe. The pulmonary vascular markings were increased, suggestive of a left to right shunt (Fig. 1).

The electrocardiogram showed sinus rhythm with a rate of 150/min. The mean frontal axis was +165°, and there was moderate to marked right ventricular hypertrophy for age.

All other investigations were normal.

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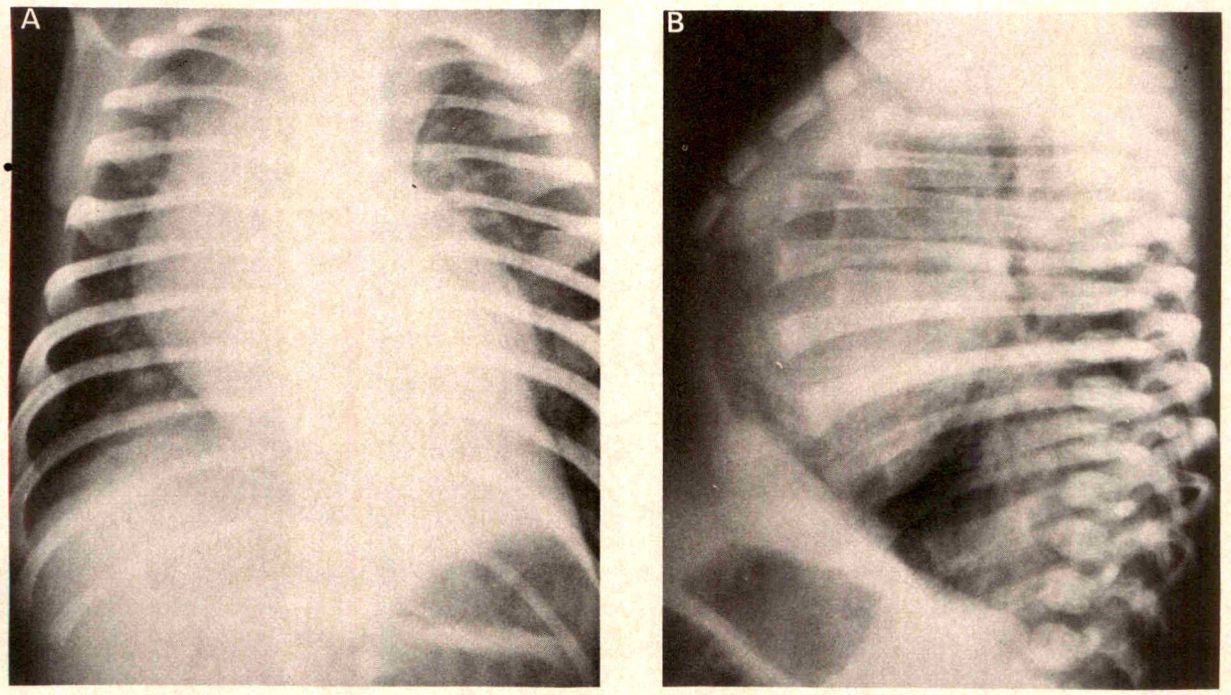

Figure 1. Anteroposterior (**A**) and lateral (**B**) chest X-ray films demonstrating the sequestrated lobe in the left lower zone, the cardiac enlargement and plethoric lung fields.

A course of ampicillin was instituted. The respiratory distress subsided after 3 days, and he remained well until the ninth day when evidence of cardiac failure developed. At this stage a poorly localized grade 1 to 2/4 systolic murmur, maximal at the left sternal edge, was audible. The pulses in the upper and lower limbs were collapsing. A repeat chest X-ray film revealed further increase in cardiac size. He responded well to digitalization over the next 48 hours. The murmur now became loudest at the left base posteriorly and extended through the second heart sound into early diastole. His general condition improved and he was discharged asymptomatic to be treated as an outpatient.

At home his mother reported slowness with feedings associated with exhaustion. On reexamination at age 5 weeks there was still evidence of mild cardiac failure. A marked precordial bulge was now noted. A grade 2 to 3/4 continuous murmur was audible at the left base posteriorly. The pulses were collapsing, the blood pressure being 115/0 mm Hg in the right arm and 125/40 in the right leg. He was readmitted and

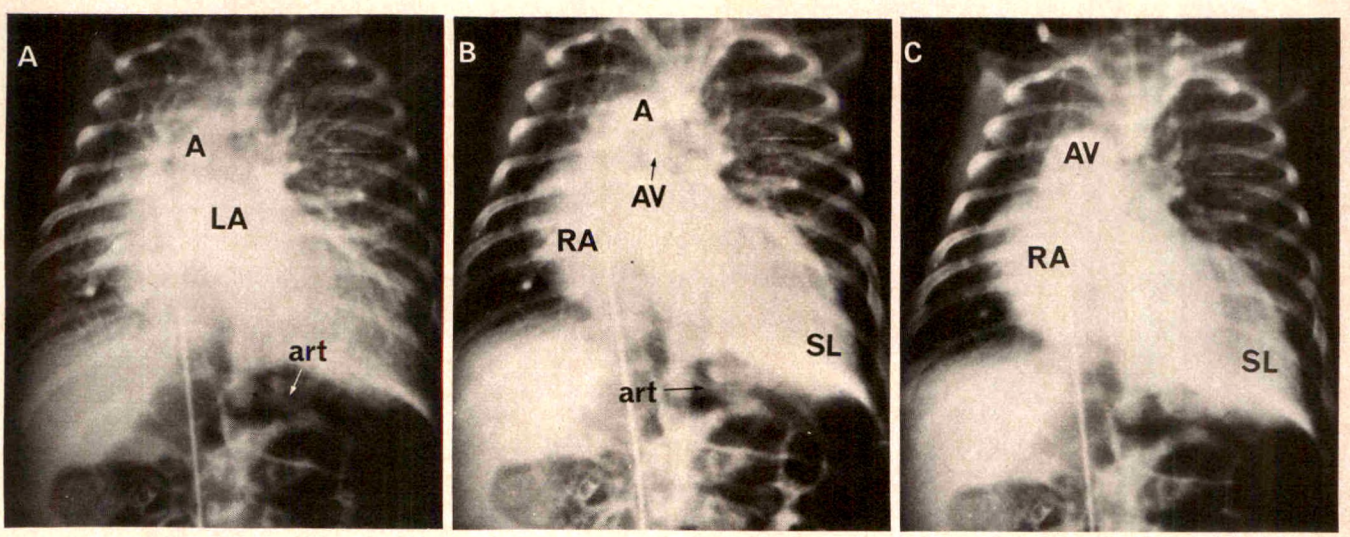

Figure 2. Angiocardiograms. **A,** early film demonstrating circulation of contrast medium through the lungs, the left atrium (LA) and aorta (A). **Arrow** demonstrates the arterial supply from the abdominal aorta to the sequestrated lobe. **B,** later film demonstrating early filling of the azygos vein (AV) which drains the sequestrated lobe. **C,** later film showing the azygos vein and right atrium filled with contrast medium. RA = right atrium; SL = sequestrated lobe.

TABLE I

Cardiac Catheterization Data

Site	Preoperative		Postoperative	
	Pressure (mm Hg)	O_2 Sat. (%)	Pressure (mm Hg)	O_2 Sat. (%)
Mid superior vena cava	...	45.5	...	63
Innominate vein	...	45	...	...
Low superior vena cava	...	93.5; 81.5	...	63
High right atrium	...	93.5	...	59
Mid right atrium	a 9; v 4	88.5	a 4	59.5
Inferior vena cava	...	65	...	67
Left atrium	a 7–9; v 6	95	a 7	97
Left pulmonary artery	10/5	92	20/10	65.5
Main pulmonary artery	45/10	89	20/12	63.5
Right pulmonary artery	25/10	90	20/10	62.5
Right ventricle	45/0	...	22/0	67

Sat. = saturation.

redigitalized, but feeding remained difficult and the cardiac failure proved more resistant to treatment on this occasion.

Cardiac catheterization: The results are presented in Table I. There was a large left to right shunt at the low superior vena caval and atrial level. The catheter passed from the low superior vena cava into the azygos vein. The gradients between the main pulmonary artery and the left and right main branches were probably related to the large pulmonary flow. Angiography demonstrated the arterial supply of the sequestrated lobe from a branch of the abdominal aorta. The venous return was by the azygos vein to the superior vena cava and right atrium (Fig. 2).

Surgical findings: Operation was postponed on several occasions because of pyrexia. In spite of a recurrent high fever (105 F), resection was performed in view of the rapid deterioration of the infant's condition at age 9 weeks.

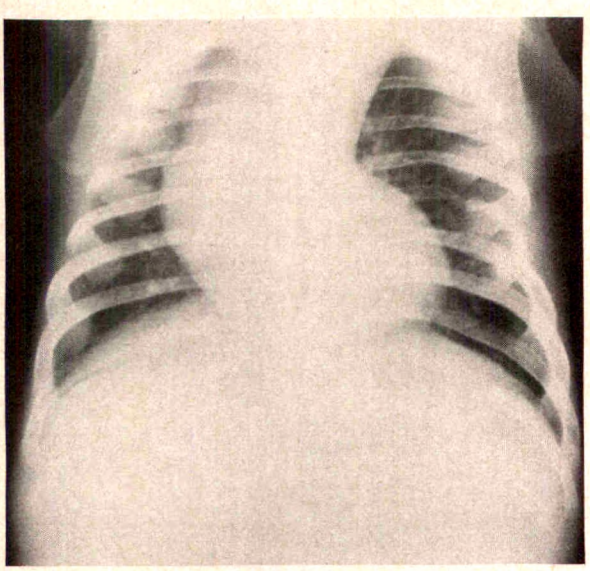

Figure 3. Postoperative chest roentgenogram.

At operation, a nonaerated pulsatile lobe of lung supplied by 2 systemic arteries arising from the aorta and passing through the hiatal ring was found. After division of these vessels the abnormal lobe shrank and the large hemiazygos vein became markedly smaller.

The surgical specimen had the characteristic features of extralobar sequestration without any respiratory passage in the hilum.

Postoperative course: The infant had an uneventful postoperative recovery, his condition improving dramatically. The fever subsided and the heart rate, respiratory rate and pulse pressure returned to normal. The murmur at the left base disappeared. Postoperative chest roentgenograms showed re-expansion of the left lower lobe with no localized consolidation. He was discharged on the ninth postoperative day at age 11 weeks. At postoperative follow-up study 2 weeks later he was extremely well and digoxin therapy was discontinued.

At age 5 months he was admitted for reinvestigation. Repeat cardiac catheterization (Table I) demonstrated a patent foramen ovale without left to right shunt. Intracardiac pressures were normal. Attempts to catheterize the azygos vein on this occasion were unsuccessful. Electrocardiogram and chest roentgenogram had returned to normal (Fig. 3).

Discussion

Sequestration of the lung was first described by Rokitansky[4] and Rektorzik[5] separately in 1861. Since that time numerous case reports have appeared which have been reviewed elsewhere.[2,6–8]

Most workers are agreed that extralobar sequestration is a congenital anomaly, but there is a wide divergence of opinion as to the origin of intralobar sequestration. These discussions are adequately reviewed elsewhere.[9–12]

The present case had the characteristic features of extralobar sequestration; namely, the arterial supply was from branches of the abdominal aorta piercing the diaphragm with the venous drainage by way of the azygos system; the pulmonary tissue was entirely separate from the normal lung and enclosed in its own parietal pleura. The unique feature was the presentation of the sequestration as an arteriovenous fistula with a large left to right shunt resulting in cardiac failure. Such a mechanism has been postulated by some authors[2] previously on the basis of clinical observations, but we believe that this is the first such case in which it has been proved by hemodynamic and angiocardiographic studies in the young infant.

Cardiac failure associated with an accessory lobe was first reported by Springer[13] in 1898; Deaton and Smith[14] reported a case of intralobar sequestration presenting as this case in a 1 day old infant whose condition improved dramatically after early surgical removal of the sequestration lobe. Solit et al.[8] described a 23 year old woman with an intralobar sequestration who showed a marked decrease in measured cardiac output after the removal of the lobe.

Congenital systemic arteriovenous fistulas presenting with cardiac failure in the neonatal period are well described. Most have been intracranial,[15–17] but other sites are less commonly described. In this infant the hemodynamic findings were similar to those of any large systemic arteriovenous fistula. Since most intralobar sequestrations are drained by way of pulmonary veins, angiocardiographic differentiation may be possible from the rarer extralobar sequestration which usually drains by way of the azygos or hemiazygos systems.

Acknowledgments

We thank Dr. T. H. Beare for referring this case for investigation and treatment and for permitting us to submit the details for publication.

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Meningococcal Pericarditis

Report of 2 Cases, 1 Complicated by Acute Constrictive Pericarditis

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Two patients with pericarditis complicating meningococcal meningitis are reported. In 1, acute constrictive pericarditis developed 1 month after pericardiocentesis for cardiac tamponade. He was successfully treated and represents the only known survivor.

Forty-three cases of pericarditis complicating meningoccocal infections have been reported, 9 of which have occurred in children. In 2, acute constrictive pericarditis developed; in 1, the entity was recognized at postmortem examination; the second case is reported herein.

Purulent pericarditis in children is infrequently encountered and, if overlooked or improperly treated, will lead to the death of the child from cardiac tamponade or sepsis. It most often occurs secondary to severe bacterial infection in the lungs, bones, kidneys, meninges and bloodstream. The bacterial organisms most frequently recovered are staphylococci, pneumococci and streptococci.

Pericarditis complicating meningococcal meningitis is infrequently encountered in children. To date, 7 cases have been reported.[1–7] Two additional cases recently encountered at the Children's Hospital of the District of Columbia form the basis of this report. One of the patients experienced rapid constriction and was successfully treated. This patient is the second to be reported on and the only known survivor of constrictive pericarditis following meningococcal pericarditis.

Case Reports

Case 1: An 11 year old white boy was admitted to a suburban hospital; he had been acutely ill for 24 hours with fever, restlessness, double vision, oliguria and extreme lethargy. His past medical history revealed that he was free of any serious disease. On admission he was semicomatose with a rectal temperature of 101.4 F. Kernig's and Brudzinski's signs were positive, and there was palsy of the right sixth nerve. Blood pressure was 100/70 mm Hg, heart rate 120 beats/min, and a pericardial friction rub was heard along the left sternal border. A chest X-ray film revealed generalized cardiomegaly (Fig. 1A). An electrocardiogram showed sinus tachycardia with S–T segment elevation in leads II, III, aVF and V_2 through V_6 (Fig. 2A). The white blood cell count was 11,500 with 85 percent polymorphonuclear leukocytes and 7 percent bandforms. Hemoglobin, hematocrit and urinalysis were normal. Examination of the cerebral spinal fluid revealed protein 160 mg/100 ml, sugar 37 mg/100 ml, and 32,400 polymorphonuclear leukocytes/ml. The blood, spinal fluid and nasopharyngeal cultures were positive for Neisseria meningitidis. The patient was treated with penicillin, ampicillin and sulfisoxazole.

On the second day atelectasis of the left lung developed. However, repeated tracheal aspirations resulted in reexpansion by the fourth day. On day 7 he continued to have a low-grade fever. Blood pressure was

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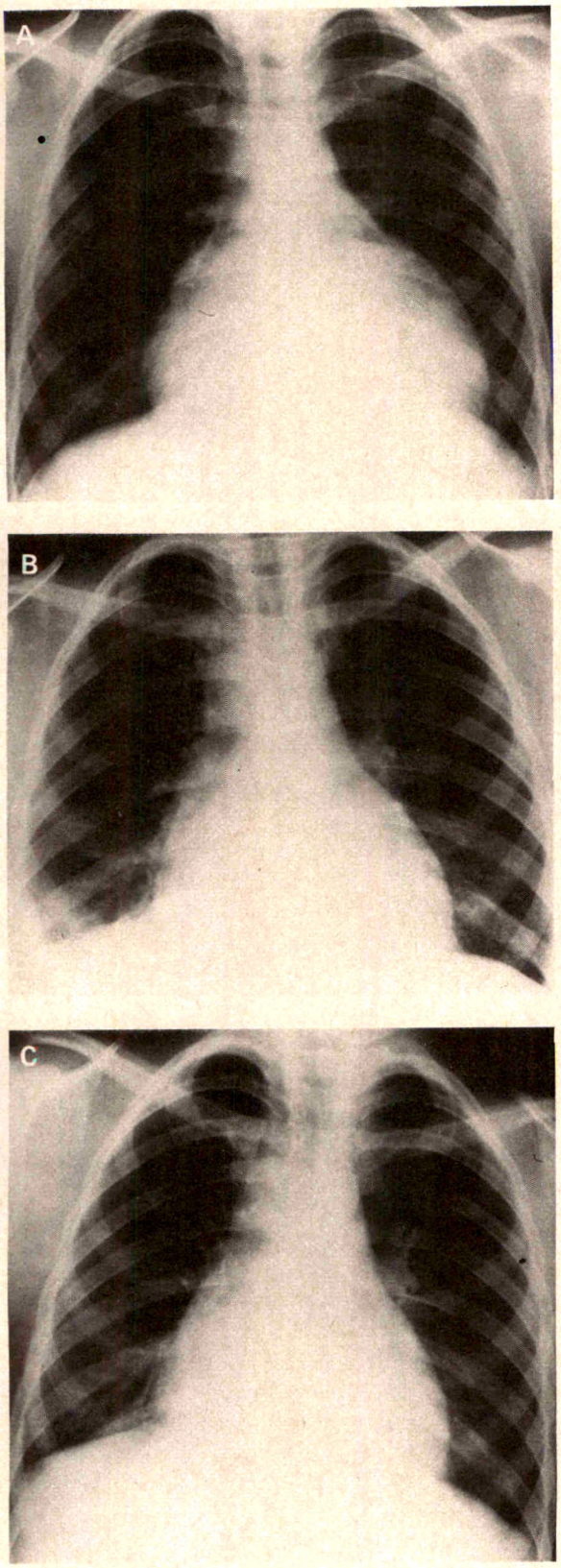

Figure 1. Chest roentgenograms. **A,** on admission, revealing generalized cardiomegaly with normal pulmonary vascular markings. **B,** on day 19, revealing a decrease in heart size with the appearance of a right pleural effusion. **C,** 1 year after pericardiectomy.

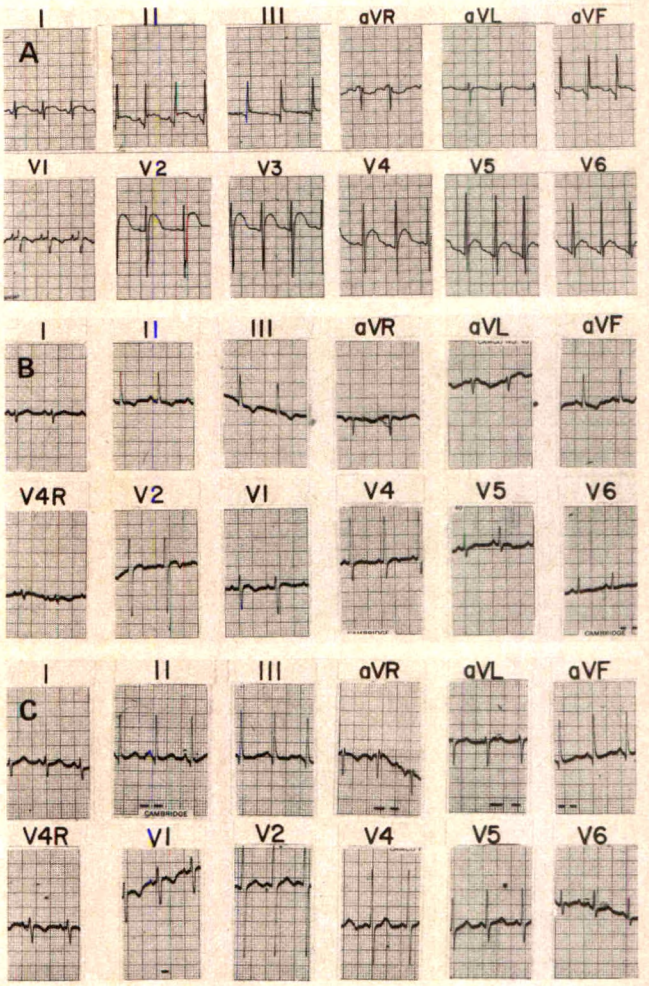

Figure 2. Electrocardiograms. **A,** at time of admission with meningitis. Note S–T segment changes of acute pericarditis. **B,** at time of acute constriction, revealing loss of QRS voltage, return of S–T segments to normal and flattening and inversion of T waves. **C,** 1 year after pericardiectomy.

104/64 mm Hg with 20 mm Hg of pulsus paradoxus. On day 9 because of an increase in heart size, tachycardia, decreasing pulse pressure, and distension of the neck veins, a pericardiocentesis was performed yielding 520 ml of serosanginous fluid resulting in immediate relief of signs of cardiac compression. Cultures of the pericardial fluid were sterile.

The patient continued to have daily temperature elevations to 102 F. On day 19, his pulse pressure began to diminish. A friction rub returned at this time, and X-ray films revealed a decrease in heart size with the appearance of a right pleural effusion (Fig. 1B). The electrocardiogram showed loss of QRS voltage, return of S–T segments to the isoelectric level, and flattening and inversion of T waves (Fig. 2B). By day 23 the pulse pressure had further narrowed, and tachycardia recurred. At this time venous distension and hepatomegaly were noted. Blood pressure was 75/55 mm Hg with 15 mm Hg of pulsus paradoxus. The heart sounds were diminished.

The boy was transferred to Children's Hospital of the District of Columbia where pericardiocentesis re-

TABLE I

Meningococcal Pericarditis in Children

Study	Age of Patient (yr)	Primary Disease	Pericarditis Onset (days)	Neisseris Meningitidis: Blood	Neisseris Meningitidis: Cerebral Spinal Fluid	Treatment: Medical	Treatment: Surgical	Constriction (Interval From Onset) (weeks)	Result
Gersony, McCracken[1]	13 mo	Meningitis	4	+	+	Ampicillin	+	0	Cured
Weis, Silber[2]	4	Meningitis	7	+	+	Tetracycline	+	3	Died
Lowe, Diamond[3]	13	Meningitis	7	+	+	Penicillin, sulfadiazine	+	0	Cured
Stamey[4]	8	Meningitis	5	0	+	Penicillin, sulfadiazine	+	0	Cured
Trace, Berkowitz[5]	13	Meningitis	5	0	+	Intrapericardial antisera	+	0	Cured
Lebowitz, Nespole[6]	3	Meningitis	3	0	+	Penicillin, sulfadiazine, chloramphenicol, steroids	+	0	Cured
Benzing, Kaplan[7]	15	Meningitis; pneumonitis	...	+	0	Penicillin	0	0	Cured
Present report	11	Meningitis	5	+	+	Gantrisin, penicillin, ampicillin	+	4	Cured*
	6	Meningitis; pneumonitis	3	0	+	Ampicillin	0	0	Cured

* After pericardiectomy.

vealed no free pericardial fluid. In the operating room a midsternotomy exposure revealed a densely adherent pericardium through which one could not discern cardiac pulsation. The pericardium measured 7 to 10 mm in thickness. With alternate sharp and blunt dissection the thickened adhesive pericardium was removed from the right ventricle and about two thirds of the left ventricle. A small portion was removed over the left atrium and atrial appendage. The orifices of the venae cavae were then freed from constricting bands. Following removal of this tissue, myocardial tone and cardiac action improved markedly. Systemic blood pressure at the conclusion was 120/80 mm Hg. Culture of the pericardial tissue revealed no growth. Microscopic examination revealed an organizing fibrinous exudate with no granulomas noted.

One year later the patient remains asymptomatic and is actively participating in sports. Physical examination is entirely within normal limits, and chest roentgenogram and electrocardiogram have reverted to normal (Fig. 1C and 2C).

Case 2: A 6 year old white girl was admitted to Children's Hospital of the District of Columbia with a 24 hour history of headache and fever and a skin rash that appeared on the day of admission. Physical examination revealed lethargy, fever of 105 F, tachycardia (150/min), blood pressure of 140/80 mm Hg with no significant pulsus paradoxus, and a diffuse petechial rash over the entire body. Neurologic examination was normal.

Laboratory data were as follows: Hemoglobin 13.1 g/100 ml, white blood cell count 11,500, with 74 percent polymorphonuclear leukocytes and 18 percent bandforms. Urinalysis, blood electrolytes and blood urea nitrogen were normal. Cerebrospinal fluid revealed 86 mg/100 ml protein, 103 mg/100 ml sugar, 416 white cells, 89 polymorphonuclears, with gram-negative diplococci on smear. Culture of the spinal fluid yielded Neisseria meningitidis. Blood cultures were sterile.

Therapy consisted of ampicillin 300 mg/kg per day intravenously. Within 24 hours the child became afebrile. Two days after admission sharp midsternal pain developed, associated with the development of a loud pericardial friction rub. Chest roentgenogram revealed slight cardiomegaly. An electrocardiogram was normal. Signs of tamponade never developed.

Because the child showed no signs of tamponade and her temperature remained normal, no pericardiocentesis was performed. The friction rub disappeared, and her heart size returned to normal. The electrocardiogram remained normal. Signs of constriction have not developed during 1 year of observation.

Comment

Purulent pericarditis accounts for approximately 30 percent of pericarditis in children. In children under 2 years of age it is by and large the most common cause of pericarditis and pericardial tamponade. After age 2 there is a decline in the prevalence of purulent infections of the pericardium, and by age 5 years through adolescence, rheumatic fever is the most frequently encountered cause.[8]

Staphylococci, pneumococci and streptococci are responsible for 56 to 77 percent of purulent pericarditis.[8,9] Meningococcal pericarditis on the other

hand is infrequently encountered and was recognized in only 18 patients of all ages in a review by Boyle et al.[10] in 1961. Since 1961 an additional 25 cases, including the two cases identified at this institution, have been reported.[11–22] Of the 43 cases reported, 9 or 21 percent have occurred in children below 15 years of age.

The age of the 9 patients with meningococcal pericarditis ranged from 13 months to 15 years (average 8 years) (Table I). All patients had meningitis; in addition, 2 had evidence of pneumonitis. In no case was pericarditis present initially. The onset of signs of pericardial inflammation developed from the third to the seventh day of the acute illness. In all cases Neisseris meningitidis was recovered from either the cerebral spinal fluid or blood, but not from the pericardial fluid. This undoubtedly is related to the fact that most of the patients were receiving therapy by the time the pericarditis became evident. In none of the cases was serologic grouping reported. Six of the 8 survivors had surgical drainage either by pericardiocentesis or pericardiostomy. Two patients survived without surgical drainage or evidence of development of tamponade.

Presently ampicillin is the drug of choice in the treatment of meningococcal pericarditis.[1,23] If signs of pericardial compression or infection persist, pericardiocentesis or pericardiostomy with drainage is mandatory.

Acute pericardial constriction: Constriction of the pericardium is a well recognized complication of tuberculous pericarditis. On the other hand, constriction complicating purulent bacterial infection of the pericardium following successfully treated suppurative pericarditis has been thought not to occur.[24] To date, 2 cases of constriction resulting from suppurative pericarditis have been reported in children, both following pericarditis caused by Neisseris meningitidis. One patient described by Weis and Silber[2] was recognized to have acute pericarditis with massive effusion. Pericardiocentesis was performed. Three weeks from the onset of the pericarditis, unrecognized constriction led to the child's death. At postmortem examination acute constrictive pericarditis with complete obliteration of the pericardial cavity by an organized fibropurulent exudate was encountered. The pericardium measured 8 to 10 mm in thickness. In the second case, our Case 1, constriction became obvious over a 4 week period; it was recognized and at operation acute constrictive pericarditis was found. Following pericardiectomy, there was a relatively uneventful convalescence followed by complete absence of any signs of cardiovascular disease 1 year later. It is likely that the persistent tachycardia and fluid retention encountered in the immediate postoperative period represented a minimal degree of myocardial failure from associated myocarditis. That this occurs has been demonstrated by Hardman and Earle[25] who have reported 78 percent incidence of interstitial myocarditis among 200 patients with fatal meningococcal infections.

Clinical implications: Infants and children receiving treatment for meningococcal infections should be observed closely for signs of pericarditis and myocarditis. Prompt recognition and treatment of a pericardial effusion with signs of cardiac tamponade may be lifesaving. Persistent signs of infection or cardiac tamponade are indications for immediate pericardiocentesis. Once the infection has been controlled and tamponade relieved, there should be careful observation for signs of acute constriction. Persistent signs of heart failure following pericardiectomy may be caused by associated myocarditis which should be treated with digitalis and diuretic agents.

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Hypersensitive Carotid Sinus Syncope Treated by Implantable Demand Cardiac Pacemaker

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A patient with hypersensitive carotid sinus syncope was treated by implantation of a permanent demand cardiac pacemaker. The observations suggest the value of demand pacing for persons whose major manifestation is significant bradycardia followed by hypotension. The potential value of this form of therapy can be tested in the individual case by temporarily stimulating the carotid sinus and electrically pacing the heart while monitoring both rhythm and mean arterial pressure.

Weiss and Baker[1] initially described hypersensitivity of the carotid sinus as the mechanism of a distinct form of syncope, and the syndrome has been recently reviewed.[2] This paper presents a case of hypersensitive carotid sinus syncope refractory to the usual medical management but responsive to implantation of a permanent demand pacemaker.

Case Report

A 43 year old service station attendant was admitted to the hospital with a 2 month history of episodic dizziness, mental confusion and syncope. He had mild diastolic hypertension, mild diabetes mellitus, a previous myocardial infarction and occasional angina relieved by nitroglycerin. With increasing activity he gradually experienced periods of intermittent dizziness lasting 5 to 10 minutes followed by mental confusion. The symptoms were not associated with a constricting collar, head or arm motion, cough or postural change. Physical findings were normal except for a presystolic apical gallop. Results of all laboratory studies were normal. During electrocardiographic monitoring, both carotid sinus areas were separately stimulated manually. Precautions included resuscitative equipment and an intravenous infusion. Asystolic periods of up to 5 seconds' duration were accompanied by a decrease in systolic blood pressure of more than 50 mm Hg during manual carotid compression.

Administration of belladona, orally, and atropine, intravenously, were ineffective. Percutaneous blockade by xylocaine of the right glossopharyngeal nerve prevented syncope and asystole during right carotid sinus compression. Due to reported complications of denervation of the carotid sinus, an alternate approach was attempted.

A temporary transvenous fixed-rate cardiac pacemaker electrode was positioned in the right ventricle, and mean arterial blood pressure was recorded on a pressure transducer. Carotid sinus stimulation without pacing produced asystole of 4 seconds' duration and a decrease in mean arterial pressure from 110 to 40 mm Hg over a 15 second period during which the patient exhibited confusion and garbled speech. Activation of the pacemaker at this point at a rate of 100/min resulted in a rise of mean arterial pressure to 60 mm Hg with clearing of the patient's mental status (Fig. 1A). Repeated stimulation of either carotid body produced only minimal depression of the mean arterial pressure. Accordingly, a permanent demand cardiac pacemaker was implanted. Carotid

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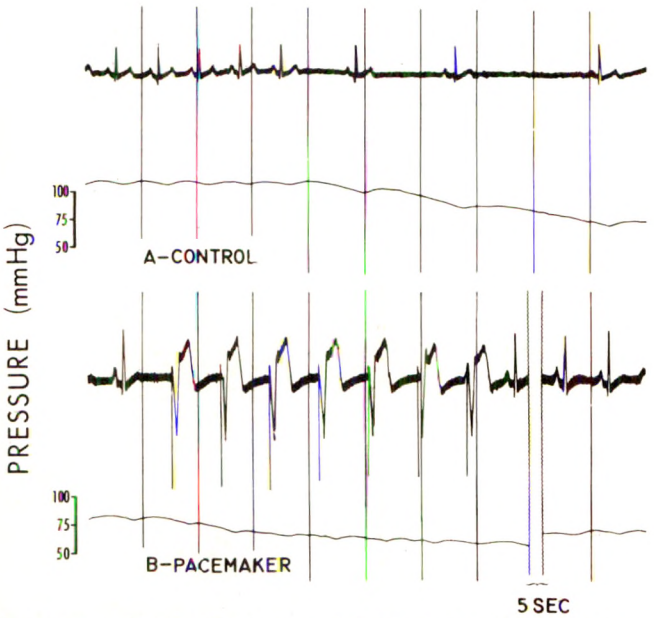

Figure 1. Electrocardiogram and mean arterial blood pressure before (**A**) and after (**B**) implantation of a demand cardiac pacemaker. In both **A** and **B** carotid sinus massage begins with the first QRS complex and continues throughout the tracing. In tracing **B**, a 5 second delay is noted. Time lines represent 1 second intervals. In tracing **A**, mean arterial blood pressure falls in concert with bradycardia, whereas in tracing **B** immediate demand pacing is followed by a transient minor decrease in mean arterial pressure.

sinus compression following operation was accompanied by immediate pacemaker-triggered systole with a transient reduction of 25 mm Hg in arterial pressure and no change in the level of consciousness (Fig. 1B).

Comment

The accepted criteria for diagnosis of hypersensitive carotid sinus syncope are a post-carotid stimulation period of asystole greater than 3 seconds' duration, or a systolic or diastolic decrease in blood presure of at least 50 mm Hg.[2,3] Both criteria were fulfilled in this patient. Additionally, he exhibited many of the conditions known to be associated with this syndrome such as diabetes mellitus, ischemic heart disease and hypertension.

Several types of therapy for hypersensitive carotid sinus syncope are available. Medical therapy has been directed toward interruption of the efferent portion of the reflex arc by vagal blockade (atropine sulfate or belladona) or by preventing the hypotensive response (ephedrine or amphetamines). Medical therapeutic failures may respond to carotid sinus radiation therapy.[2] Xylocaine block of the reflex arc has been accepted as a prerequisite to successful surgical intervention.[2,4] Adventitial stripping of the carotid artery[5] and peripheral[6] or intracranial section of the glossopharyngeal nerve[7,8] have each been advocated. Unsatisfactory results with the surgical approach have included recurrence of symptoms,[9] recurrence of carotid sinus hypersensitivity without syncope[10] and at least 1 documented case of fatal hypertension.[11]

On the basis of this case reported herein, an additional form of therapy is available in the effective control of this type of hypersensitive carotid sinus syncope. As shown, the use of a temporary pacemaker for control of the changes in blood pressure and cardiac rhythm provides a good estimation of the effectiveness of permanent demand pacing. The complications of permanent pacemaker placement are well known.[12] These complications seem acceptable in the prevention of unpredictable syncope.

Acknowledgment

We are indebted to Lawrence D. Hughes, MD, Dunellon, Fla., for the referral of this patient.

Addendum

Since the completion of this study and the manuscript reporting it, a similar case has been reported by Voss and Magnin.[13] Their report confirms the efficacy of this form of management in hypersensitive carotid sinus syncope.

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Observations on Second Degree Atrioventricular Block, Including New Criteria for the Differential Diagnosis Between Type I and Type II Block

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Since type I atrioventricular (A–V) block tends to be temporary and does not give rise to prolonged asystole, and type II A–V block tends to be progressive, ultimately leading to complete block and Adams-Stokes attacks, it is important to identify the type in each patient with acute or chronic second degree A–V block. The usual definition of these 2 types needs expansion. This new definition is given and new criteria are presented to permit differentiation of the 2 types of A–V block even in the presence of (1) incomplete A–V dissociation with single ventricular captures and (2) persistent 2:1 A–V block. The different roles and sites of concealed conduction in the 2 types of A–V block are defined.

In type I, concealed conduction occurs within the region of block and depresses subsequent conduction, occasionally leading to blockage of consecutive atrial impulses. In type II, concealed conduction occurs down to the region of block, discharging subsidiary junctional pacemakers and thus preventing their escape. The frequent association of type II A–V block with bundle branch block and ventricular escapes with normal retrograde conduction (unidirectional block) is emphasized. Concealed retrograde conduction across the region of unidirectional block facilitates antegrade A–V transmission (early ventricular captures, supernormal phase of A–V conduction). The evidence is reviewed for placing the lesion causing type II A–V block below the A–V node; this is based on correlation of electrocardiographic findings, including His bundle recordings and anatomic data. Exceptions to the rule occur occasionally but should not lead to abandonment of the electrocardiographic classification of second degree A–V block into type I and type II because the distinction has proved of great value for clinical orientation.

Two types of second degree atrioventricular (A–V) block were recognized independently in 1906 by Wenckebach[1] and Hay[2]; they were classified by Mobitz[3] as type I and type II in 1924. Type I A–V block was defined as that type of second degree A–V block in which complete failure of A–V conduction is preceded by several beats with progressive lengthening of A–V conduction time, whereas blockage occurs without any warning in type II and the conduction time of conducted beats remains constant. In view of the clinical significance of type II A–V block, recognized by Mobitz[3] as "the first step to Adams-Stokes attacks and complete, permanent dissociation," it is strange that the differentiation of

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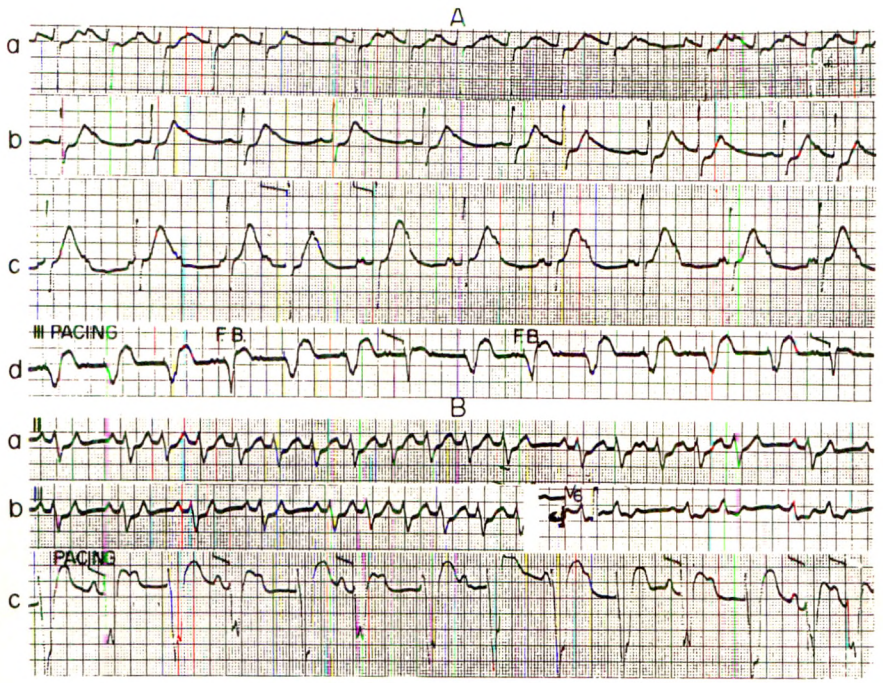

Figure 1. **A,** recent posterior wall infarction, type I A–V block. Segments **a** to **c,** monitor lead; **d,** lead III. Segment **a** shows Wenckebach periods; in the middle portion there is 7:6 A–V block with the P–R interval increasing from 0.20 to 0.32 second. **b,** 1 week later; 2:1 changing to 3:2 A–V block with the P–R interval increasing from 0.22 to 0.28 second. **c,** after isoproterenol administration; incomplete A–V dissociation, rate of junctional pacemaker 53; the P–R interval of the 2 capture beats varies inversely with the preceding R′–P distance. **d,** incomplete A–V dissociation during right ventricular endocardial pacing; the P–R interval of the fusion beats (F.B.) and capture beats varies inversely with the R′–P distance. **B,** recent anteroseptal infarction, intraventricular block, type II A–V block. **a,** lead II, 12:11 and 6:5 block with constant P–R interval (0.19 second). **b,** in lead II there is 2:1 and in V_6, 3:2 A–V block with very slight increase (0.02 second) of P–R interval. **c,** right ventricular endocardial demand pacing; conducted beats have a constant P–R interval regardless of the R′–P distance.

the 2 types of second degree A–V block has not received more attention. This may partly be due to the imperfect definition of type I block. Evidently, the criterion of gradual and progressive development of A–V conduction failure does not permit identification of the type of block present in cases with incomplete A–V dissociation and isolated ventricular captures; it also does not permit classification of the block in persistent 2:1 A–V response, a common form of A–V block.

It is the purpose of this report (1) to expand the definition of type I block so as to permit identification of the type of block in cases with incomplete A–V dissociation; (2) to point out methods of influencing A–V conduction that will permit classification in cases of persistent 2:1 block; (3) to examine the mechanism of high grade A–V block; and (4) to discuss the different role of concealed conduction in the 2 types of block. In addition, the frequent association of type II A–V block with intraventricular block and with a supernormal phase of A–V conduction will be illustrated. Finally, the site of the conduction impairment will be discussed, and the electrocardiographic and anatomic evidence for the usual infra A–V nodal localization of type II A–V block will be presented, both when it occurs in chronic A–V block of Adams-Stokes disease and in acute A–V block associated with recent myocardial infarction.

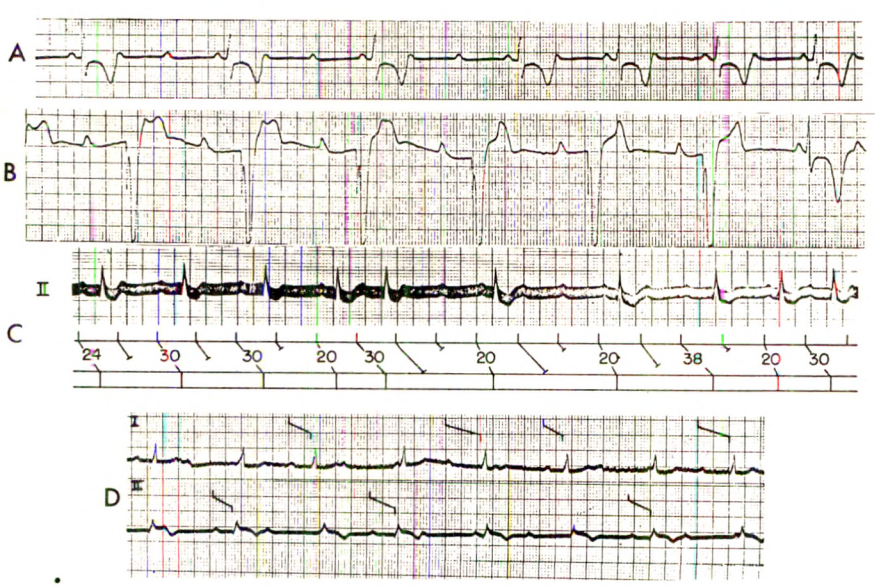

Figure 2. **A,** chronic type II A–V block; monitor lead showing 3:1 and 2:1 block with constant P–R (0.16 sec.). **B,** same patient; endocardial right ventricular demand pacing with 1 late capture (last beat). **C,** type I A–V block; lead II showing 2:1, 3:2 and 3:1 A–V block with varying P–R interval (0.20 to 0.38 second) and evidence of concealed conduction (see diagram). **D,** recent posterior wall infarction; leads I and II showing second degree A–V block, incomplete A–V dissociation; rate of junctional pacemaker is 54. Note the long P–R interval of early capture beats and the shorter P–R interval of late capture beats indicating type I A–V block.

Observations

Identification of the type of second degree A–V block in the presence of A–V dissociation with single ventricular captures: If ventricular capture beats occur at various times in the subsidiary pacemaker cycle, comparison of the A–V conduction (P–R) intervals of the captures provides a clue (Fig. 1 and 2). On the one hand, variations in these P–R intervals with an inverse relationship between R′–P and P–R suggest type I block; on the other hand, a constant A–V conduction time for all the captures despite significant variations in their timing (R′–P) indicates type II block.

The variations of the P–R interval of the ventricular capture beats in type I can be explained by the various states of refractoriness of that part of the pathway traversed by the conducted capturing atrial impulse which was also used by the preceding impulse of the subsidiary pacemaker. This preceding impulse could be either the antegrade impulse or a concealed retrograde impulse.

Captures in incomplete A–V dissociation in the presence of type II A–V block usually occur exclusively as late captures, and without marked prolongation of the P–R interval. The failure of slightly earlier atrial impulses to be conducted and to capture the ventricles (with a longer P–R interval) is further evidence of type II A–V block (Fig. 2B). Rarely, in type II, very early captures can be observed in addition to, or instead of, late captures, probably due to a supernormal phase of conduction (Fig. 3; also see Fig. 10).

2:1 A–V block: 2:1 A–V block may occur with either type I or type II block. Which of the 2 types is present can usually be determined by prolonged observation that reveals a spontaneous change in the conduction ratio (Fig. 1 and 2), or by changing the atrial rate and noting the concomitant change in A–V conduction (Fig. 4 to 6; see also Fig. 8). The effects of exercise and atropine have been pointed out by Wenckebach and Winterberg[4] and stressed by Gilchrist.[5] Moderate acceleration of the atrial rate tends to decrease the A–V block in type I and to increase it in type II. A similar effect, leading to enhancement of A–V conduction, can be seen in Figure 4, which was obtained after intravenous administration of isoproterenol in a patient with recent posterior wall infarction and type I A–V block. In contrast, a moderate increase of the atrial rate by endocardial atrial pacing at the time of 1:1 A–V conduction produced type II second degree A–V block in a patient with chronic intermittent block and predominant 2:1 A–V conduction (Fig. 5). In another patient (Fig. 6), carotid sinus pressure performed at the time of 2:1 A–V block produced sinus slowing with temporary 1:1 and later 3:2 A–V conduction without significant changes of the P–R interval, indicating the presence of type II A–V block. A similar effect in a patient with incomplete A–V dissociation is

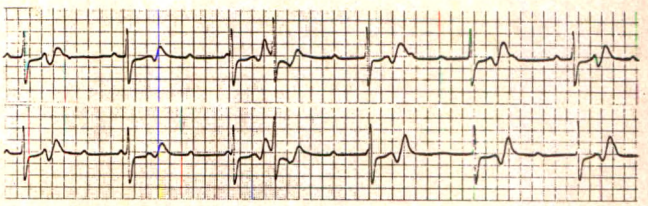

Figure 3. Intraventricular and second degree type II A–V block were present in previous and in subsequent records. Monitor lead, continuous record (last beat of **upper strip** repeated as first beat in a **lower strip**), showing incomplete A–V dissociation; there are only early captures (fourth beat in both strips) with the same timing of P. Note that the contour of the subsidiary pacemaker beats is very similar to that of the capture beats.

illustrated in Figure 7. Thus, it would appear that the dromotropic effect of the intervention in type I and the chronotropic effect in type II determine the change in A–V transmission. Finally, in a patient with a history of Adams-Stokes attacks (Fig. 8), ventricular "parasystolic" pacing was used during 2:1 A–V block; this permitted captures of the natural impulse at a constant P–R interval which was unrelated to the R′–P interval. This effect would suggest type II A–V block if concealed retrograde conduction of the artificial impulses can be assumed.

Recently, the method of recording His bundle potentials has demonstrated[6–9] the anticipated[10–15] infranodal site of type II A–V block. Hence, the presence of His bundle potentials after the blocked P wave in 2:1 A–V block (Fig. 6C) is highly suggestive of type II block, although it does not exclude the possibility of the rarely occurring infranodal type I block.[7]

The duration of the P–R interval in 2:1 A–V block does not permit distinguishing between type I and type II block. Although A–V conduction is frequently normal in type II and usually prolonged

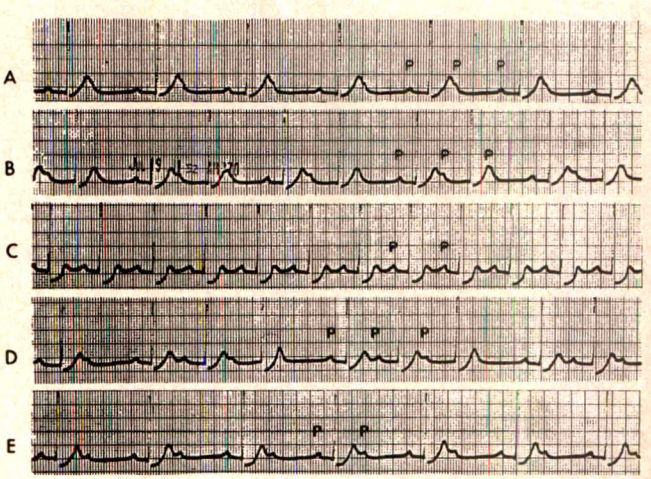

Figure 4. Recent posterior wall infarction, monitor lead. **A,** 2:1 A–V block (P–R interval 0.28 second). **B to E,** after intravenous administration of isoproterenol, show change in A–V conduction. Wenckebach periods in **B** and **D** are indicative of type I A–V block.

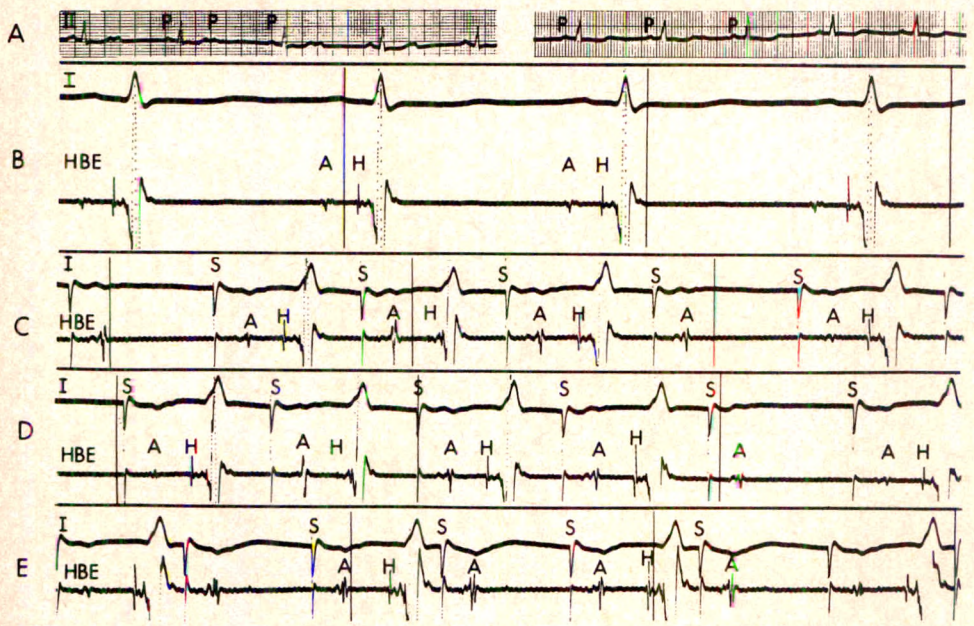

Figure 5. **A,** chronic intermittent 2:1 A–V block, P–R interval 0.18 second. **B,** His bundle electrogram (HBE) during 1:1 A–V conduction. **C to E,** during atrial pacing (S) (rate 100/min in **C** and **D,** 136/min in **E**) show type II second degree A–V block (4:3 and 5:4). A–H and H–V intervals remain constant, no His deflection (H) is recorded after blocked atrial impulse (A). **Block is localized** in lowest portion of A–V node or upper part of His bundle.

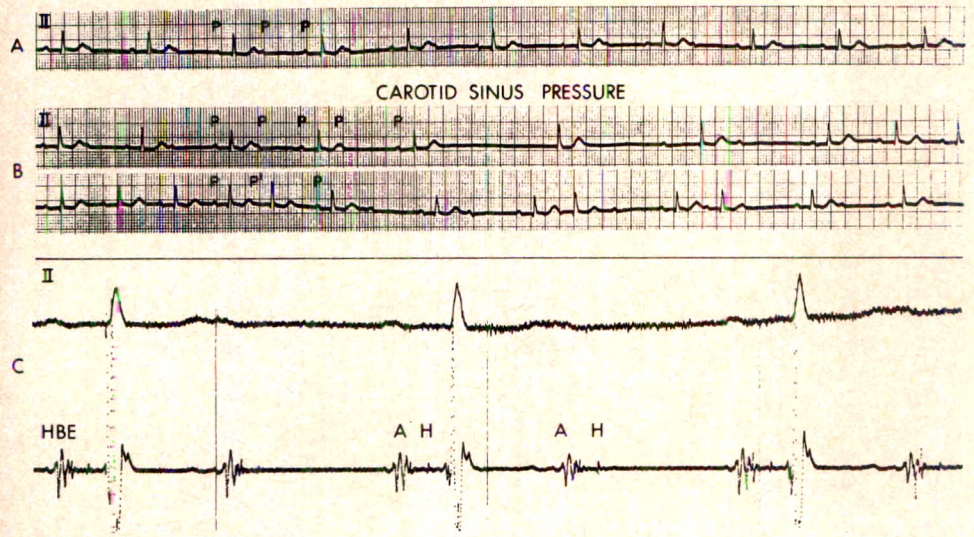

Figure 6. **A,** chronic 2:1 A–V block, P–R interval 0.24 second. **B,** carotid sinus pressure, continuous tracing (last beat in **upper tracing** repeated as first beat in **lower** strip); after marked slowing of atrial rate (probably S–A block) there is junctional escape, later 1:1 A–V conduction, followed by 3:2 A–V block with constant P–R interval indicative of type II block. **C,** His bundle electrogram during 2:1 A–V block shows H after the blocked atrial impulse with the same A–H interval (nodal transmission time) as the conducted impulse. The site of the A–V block is below the A–V node.

in type I A–V block, it may be prolonged in type II when there is either a concomitant lesion in the A–V node or delayed H–V conduction due to delay either in the His bundle or in the main bundle branches.[7,8,16,17]

Slight shortening of the P–R interval (not exceeding 20 msec) in the beat after the intermittence can be observed with A–V block otherwise characteristic of type II, in that the P–R interval is constant in all other beats and there is no lengthening of this interval before a dropped beat (Fig. 1B). Occasionally this slight shortening of the P–R interval in the beat after intermittence may indicate occurrence of an escape following the pause, but the phenomenon may also be observed in cases where escapes can be ruled out. In the latter instance, it may be difficult to identify the type of block should there be a 3:2 conduction ratio.

High degree A–V block: Mobitz[3] and Wenckebach and Winterberg[4] pointed out that blockage of 2 or more consecutive atrial impulses, that is, 3:1 or a higher degree of block, is common in type II block. However, such multiple blockage may also occur in type I under 2 conditions:

1. As a temporary phenomenon due to isolated or repetitive concealed conduction.[12,18] This is illustrated by Figures 2C and 9 where 3:1 block actually represents an abortive 3:2 block.

2. With rapid atrial rates due to the development of 2 regions of block in the A–V junction, an upper physiologic region of 2:1 conduction and a lower region of type I block. This is best exemplified by cases of atrial flutter after digitalization.[19] Here, type I of the lower region is responsible for the characteristic structure of Wenckebach periods of the ventricular responses. Thus, the criterion of

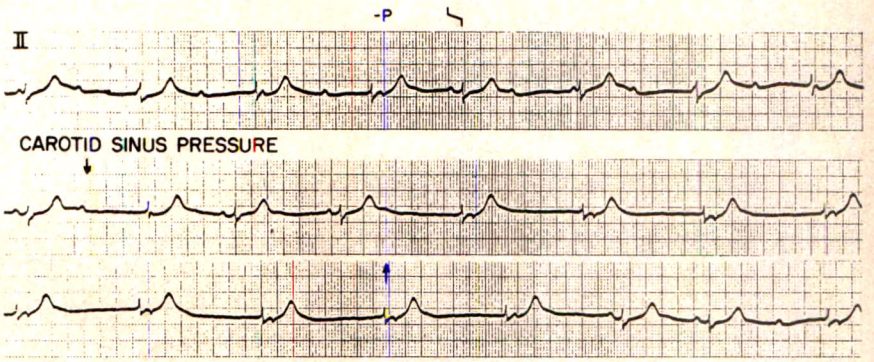

Figure 7. Chronic A–V block, Adams-Stokes disease. **Top strip** shows incomplete A–V dissociation (A–V junctional pacemaker, rate 41/min) with 1 atrial capture (—P) and 1 late ventricular capture. Carotid sinus pressure (continuous tracing, last beat of **middle strip** repeated as first beat of **bottom strip**) produces sinus slowing with 1:1 A–V conduction (third and fourth beats), followed by A–V junctional rhythm with retrograde conduction; when sinus rhythm is resumed there is type II 3:2 A–V block, P–R interval 0.18 second. Arrows indicate onset and end of carotid sinus pressure.

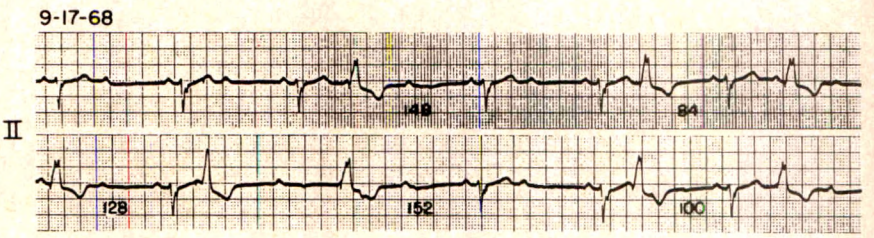

Figure 8. Chronic 2:1 A–V block, intraventricular block. Endocardial **right ventricular** fixed rate pacing (rate 34/min) elicits a response whenever pacemaker impulse falls outside refractory period of conducted beat. The P–R intervals of conducted beats are constant (0.20 second) regardless of R'–P, suggesting type II A–V block.

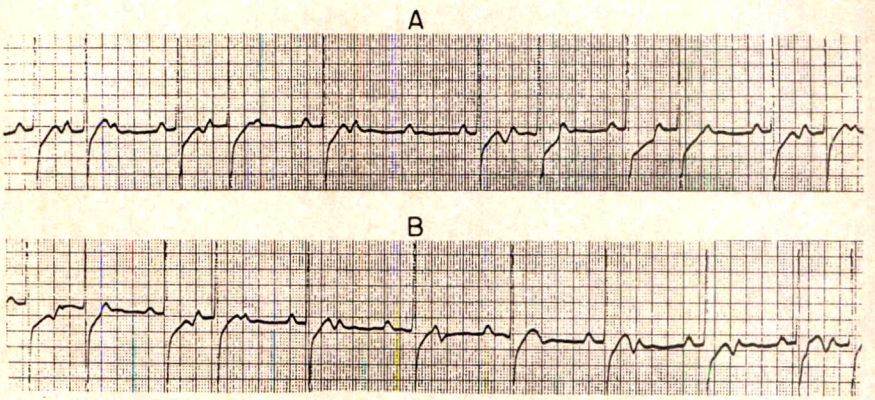

Figure 9. Recent posterior wall infarction, monitor lead. In **A,** there is type I 3:2 A–V block interrupted by 3:1 block, a result of concealed conduction (abortive 3:2 block). In **B,** 3:2 A–V block is followed by 2:1 A–V block with various P–R intervals due to differences in concealed conduction of the blocked atrial impulse.

multiple blockage cannot be relied upon in making the diagnosis. It indicates type II block only if the P–R interval remains constant with various ratios of atrial to ventricular beats (Fig. 2A).

Concealed conduction in second degree A–V block: Concealed conduction occurs in both types of A–V block. In type I it takes place within the region of block (usually within the A–V node) and influences subsequent conduction (Fig. 2, C and D, and 9); in type II it occurs in the conduction path leading to the region of block. In cases in which type II block is associated with bilateral bundle branch block (see later), one can assume that concealed conduction of the atrial impulses is present not only in the A–V node and His bundle but also continues into the bundle branches. Under such circumstances, the absence of supraventricular escapes is explained by the repetitive concealed discharge of a potential subsidiary pacemaker.

In cases of high degree A–V block with preserved retrograde conduction (see later), concealed retrograde conduction across the region of unidirectional block may be followed by a change in conductivity, presumably a supernormal phase, which permits propagation of the subsequent antegrade impulse (early capture) (Fig. 3 and 10) and, in cases of high grade type II block, may sometime initiate longer periods of 1:1 antegrade conduction with a constant and normal P–R interval [20,21] (see Fig. 12).

Association of type II A–V block with bundle branch block and with normal retrograde conduction (unidirectional A–V block): The frequent association of type II A–V block with intraventricular block has been recognized recently.[11–15,22] Both electrocardiographic observations and autopsy findings suggest that second degree or complete A–V block develops in such cases as a result of bilateral bundle branch block (see later). If ventricular ecapes occur in type II second degree A–V block, or if the block progresses, temporarily or permanently, to complete A–V dissociation, retrograde propagation of the ventricular impulse (atrial capture) is frequently observed and usually

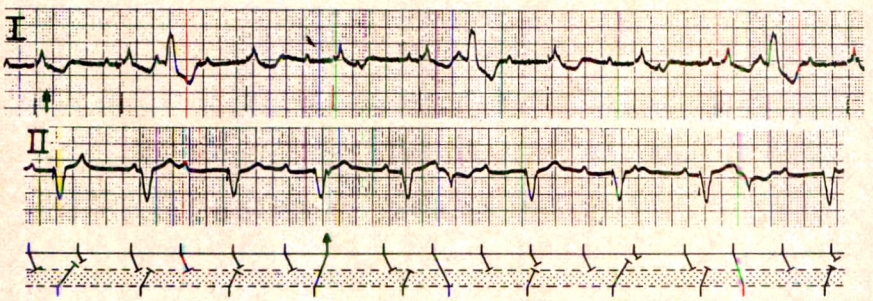

Figure 10. Recent myocardial infarction, left bundle branch block and type II A–V block, right ventricular demand pacing. Only early ventricular capture beats are seen, explained by supernormal phase of conduction following concealed retrograde conduction across region of unidirectional block (**stippled area** in diagram). Note atrial capture beats (indicated by **arrows**).

takes place with a normal V–A conduction time[23,24] (Fig. 7, 10 and 11). Retrograde conduction may be masked and remain concealed because rapid atrial activity keeps the A–V junction refractory by means of concealed antegrade conduction of the "blocked" atrial impulses (Fig. 11). The operation of this mechanism can be demonstrated by pacing the ventricle at a rate exceeding the spontaneous atrial rate, resulting in a 1:1 retrograde response[24] (Fig. 11). Furthermore, if the rate of ventricular pacing is then gradually decreased, "reversed incomplete A–V dissociation" with atrial captures develops (Fig. 11), and sometimes an inverse relationship of R′–P′ and P–R′ intervals can be demonstrated. This indicates concealed conduction of the "blocked" atrial impulses to the region of unidirectional block. As stated, concealed retrograde conduction may facilitate subsequent antegrade conduction and explain early captures, presumably during a supernormal phase of conduction (Fig. 10 and 12).

The site of the lesion responsible for chronic type II A–V block: The autopsy findings in chronic A–V block[25–34] for a long time have indicated that A–V block may be the result of bilateral bundle branch block rather than a lesion in the A–V node. The indirect electrocardiographic evidence for such an infra A–V nodal localization, as discussed, is 2-fold: First, the frequent association of type II A–V block (the forerunner of complete A–V block) with intraventricular block—often indicative of bilateral bundle branch involvement. Second, the frequent association of type II A–V block with normal retrograde conduction (unidirectional block) and evidence of concealed antegrade conduction. Thus, the site of the lesion responsible for type II A–V block was predicted to be distal to the A–V node.[10–15] As stated, this was confirmed recently by direct evidence obtained from the recording of His bundle potentials (Fig. 5, 6 and 11). Narula and Samet,[7] in 12 cases of type II chronic A–V block, showed His bundle potentials following the blocked P waves and, in most of them, a normal nodal transmission time (A–H interval).

In the less common cases of type II A–V block, those without intraventricular block, His bundle recordings have also localized the block below the

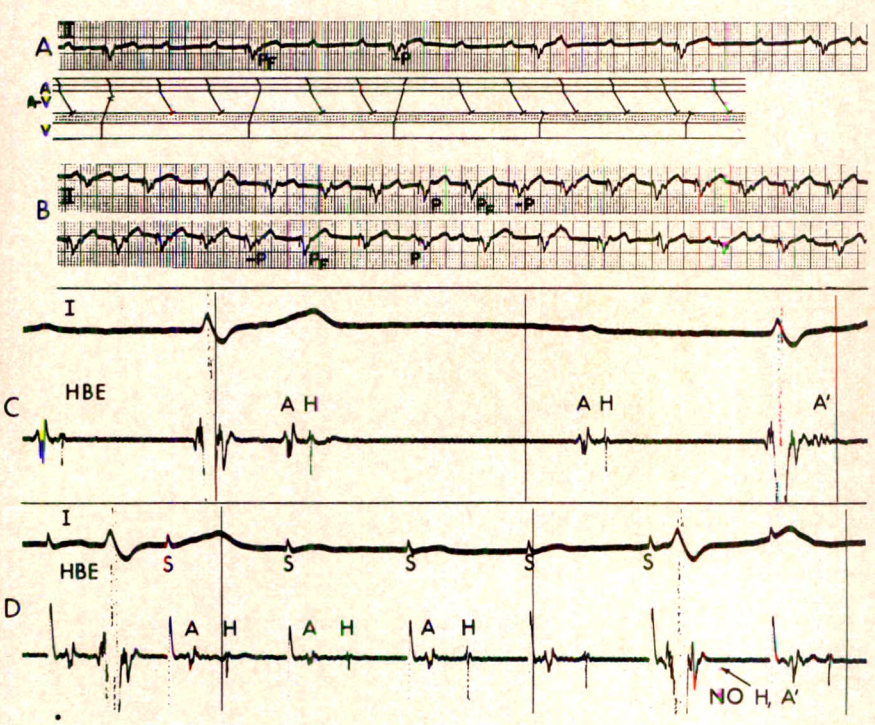

Figure 11. From a patient with type II second degree A–V block that progressed to complete A–V block. **A,** right ventricular endocardial pacing, rate 34/min; there is A–V block with V–A conduction (unidirectional block); occurrence of atrial capture (—P or P_F) depends on P–R′ distance, indicating concealed conduction of blocked atrial impulses into the pathway of retrograde conduction. **B,** after increasing rate of ventricular pacing (100/min) above sinus rate, 1:1 retrograde conduction ensues (R′–P′ 0.14 second). **C,** average atrial rate 70/min, ventricular rate 33/min, complete A–V dissociation. The His bundle electrogram reveals H after each blocked sinus impulse, with normal nodal transmission time (A–H 90 msec); after the last beat retrograde P (A′), retrograde H must be hidden in QRS complex. **D,** during atrial pacing (rate 150/min), A–H time increases to 135 msec. Note the absence of A′ and absence of H after the last ventricular complex **(arrow),** indicating simultaneous concealed antegrade and retrograde conduction with interference in the A–V junction, similar to the events after the first ventricular beat in strip **A.** A retrograde H must be hidden in this QRS.

A–V node[7] (Fig. 6). Here, in agreement with anatomic findings, the A–V block appears to be due to a lesion in the common bundle above its terminal bifurcation rather than due to intermittent bilateral bundle branch block. Undoubtedly this is true in cases in which either escape beats during second degree block or ventricular beats after establishment of complete A–V dissociation maintain the "supraventricular" appearance of the conducted beats (Fig. 6 and 7). Evidently, when A–V dissociation occurs in patients with both second degree A–V block and bundle branch block and the pattern of the ventricular complexes does not change, one can no longer assume a "supraventricular" pacemaker and simultaneously postulate that the A–V dissociation is the result of bilateral bundle branch block. Here the alternate assumption must be considered, namely, that the ventricular pacemaker during A–V dissociation originates in a bundle branch beyond the region of block (Fig. 3).

A–V block in recent myocardial infarction: The distinction between type I and type II A–V block is of the utmost importance in patients with recent myocardial infarction (Fig. 1, 2D, 4, 9 and 10) since it involves a prognostic assessment and also becomes a guide to the indication for prophylactic pacing.[14,15,35–41] The acute form of type II A–V block, observed during continuous monitoring in recent anterior wall myocardial infarction (Fig. 1B), has only recently been recognized. As in chronic A–V block, the association of type II A–V block with prolonged asystole (Adams-Stokes attack) is observed in contrast to its absence in type I A–V block. Type I A–V block is much more common in posterior (inferior) wall myocardial infarction and tends to be temporary. As stated, type I can be recognized as such not only when Wenckebach periods lead to occasionally dropped beats (Fig. 1Aa, 4, B and D, and 9) but also during predominant A–V dissociation with only occasional ventricular captures (Fig. 1A, c and d, and 2D). Second degree 2:1 block is a frequent intermediate form. It should not be classified as type II A–V block if it alternates with, or is preceded or followed by, lesser degrees of type I A–V block (Fig. 1A and 4). Anatomic studies have shown that the association of acute anteroseptal myocardial infarction and A–V block is due to bilateral bundle branch involvement rather than to involvement of the A–V node or His bundle.[34,42,43] The different localization of type I and type II A–V block in recent myocardial infarction has been confirmed by the recording of His bundle potentials.[9] Actually, in anterior wall myocardial infarction second degree or complete A–V block may be heralded by the appearance of bundle branch block, usually right,[44–48] rather than by a lesser form of A–V block.

Comments

At present it is not known why depression in the conduction system below the A–V node tends to give rise to the type II variety in contrast to the occurrence of type I block when A–V nodal tissue is depressed. However, the type I form of block can also occur in the His bundle[7] and in the bundle branches,[49–51] although the increments in conduction time are smaller. In fact, the small increments characteristic of type I block below the A–V node may be missed in recordings with the usual camera speed; thus, some cases interpreted as type II A–V block may actually be cases of type I infranodal block. Furthermore, combinations of type I and type II A–V block do occur. Thus, type I A–V block in the proximal portion of the conduction system may be combined with type II A–V block in

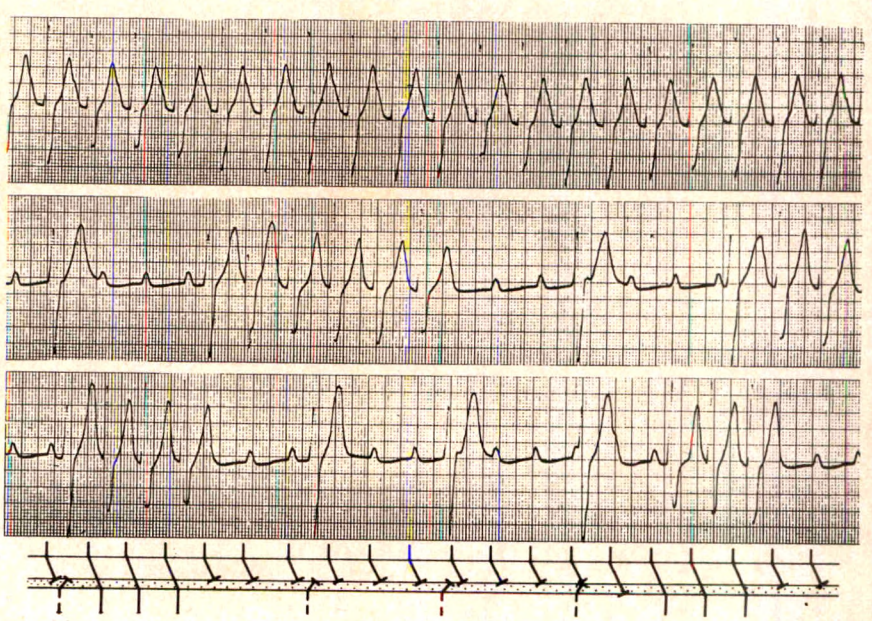

Figure 12. Stokes-Adams disease due to high grade A–V block and right bundle branch block; retrograde conduction was present in records with slower sinus rate and during rapid ventricular pacing. Atrial rate 110/min; rate of ventricular pacemaker in **middle strip** 34/min, in **bottom strip** 40/min; runs of 1:1 A–V conduction are initiated when the sinus P wave falls on top or on the descending limb of the T wave of the ventricular pacemaker. Note that the last run of conducted beats appears to follow concealed antegrade conduction as indicated in the diagram.

the distal portion, or type II block of antegrade conduction may be combined with type I block of retrograde conduction. The former has been demonstrated with rapid atrial pacing,[7,8] the latter with rapid ventricular pacing[24] in patients with type II A–V block.

Recordings of the electrical activity of the His bundle and bundle branches in man have greatly increased our knowledge regarding the site (or sites) of A–V block and its type. Together with the experimental approach[52,53] they can be expected to provide further clarification regarding the nature of type II block. However, it must be recalled that the correlation of simple observations made by means of the standard surface electrocardiogram when combined with the clinical course of the patient and the anatomic findings at necropsy established the clinical usefulness of the distinction between type I and type II A–V block long before the recent advent of intracavity electrocardiogram recordings. The latter confirmed that type I A–V block represents primarily A–V nodal block and type II A–V block indicates block below the A–V node. The exceptions to this rule cast no doubt on the validity of this concept and should not suggest abandonment of an electrocardiographic classification[7] that has proved its great value in clinical orientation in the past.

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A Critical Appraisal of Ballistocardiography

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The ballistocardiograph is an apparatus for recording body motion, generally in a head–foot direction, secondary to cardiovascular phenomena. The first records were obtained by Gordon[1] in 1887, and since then there have been many efforts to determine the mechanisms of these body movements and their relation to cardiovascular events. Useful clinical interpretations of the abnormal wave forms that occur in patients with heart disease have been difficult to achieve. In spite of a vast amount of investigative work over the past 50 or so years, the technique has not reached a satisfactory state of scientific or clinical acceptability. Many investigators, particularly in recent years, have avoided ballistocardiographic studies, and in the medical community there is a fair amount of skepticism concerning the merits and clinical uses of the technique. Several factors have contributed to these negative attitudes.

Problems in Methodology

Probably the most important problems have been those of methodology. Many of the published reports have been concerned with techniques of recording the movements of the body, and various methods have been proposed. Consequently, the contours of the ballistocardiogram have varied according to the techniques employed, and conflicts have arisen about the nature of the "true" ballistocardiogram. Confusion on methodology can often be attributed to lack of understanding of (1) the physical problems related to coupling of the body to the platform from which the motion is sensed (whether this be a bed which a patients rests upon or a platform which rests upon a patient); (2) the physical characteristics of the transducer used to record the motion; and (3) the relations between displacement, velocity and acceleration of body motion.

Physical problems concerning the accurate registration of body movement: These problems, discussed by Talbot and Harrison[2] in 1955, are still not fully appreciated. The latters' studies demonstrated that the body has a tendency to oscillate on the platform due to its elastic coupling, thus producing artifacts in the records. These artifacts can be made negligible by reducing the weight of the moving part of the bed to less than 10 lb, eliminating or making minimal use of bed damping, and keeping the period of the bed below 0.3 Hz. When these principles are observed, such a platform closely follows the movements of the body, and the records can be satisfactorily interpreted with relative ease. Lack of proper recognition of physical difficulties has rendered almost useless a number of published studies.

There are now several different ways of constructing suitable platforms. Lightweight beds can be made of honeycomb aluminum and can be suspended in different ways yet still yield essentially the same records. The platform can be hung by long cables from the ceiling so that the period of the bed is near the ideal figure cited. More practically, the bed can be equipped with an air-bearing type of suspension. Records obtained with this technique are essentially identical to those obtained during weightlessness,[3,4] thus confirming that these traces represent the ideal form of the ballistocardiogram. Since the ultra-low frequency ballistocardiogram has been shown to reflect accurately the ideal body motion, this method is clearly the most advantageous one for recording ballistocardiograms.

Understanding of the mathematical relationships between velocity, acceleration and displacement: Such understanding is essential for the correct interpretation of ballistocardiograms. Motion can be recorded by any or all 3 types of sensors, depending upon the purpose of the investigation. Physicians often poorly appreciate that all 3 types of records really contain the same information, since velocity is the first mathematical time derivative of displacement, and acceleration is the second time derivative of displacement. There-

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fore, the informational content in all 3 records is the same, and the only basis for choosing a particular type of sensing transducer is the purpose of the investigation. Often some abnormalities are more easily visualized in one type of recording than another. It is now generally agreed that the acceleration record is probably the most useful, since abnormalities are more easily recognized in these records than in the velocity or the displacement traces.

Problems Related to Aim of Investigator

The second problem that has resulted in a negative attitude toward ballistocardiography is related to the purpose or aims of the investigators. A few examples are worth mentioning. Initially, a great deal of attention was directed toward the calculation of stroke volume. Reasonable results were obtained in normal subjects; however, the technique was generally not successful in disease states in which the information concerning stroke volume would be particularly useful. For example, studies revealed a fairly close correlation between stroke volume and that calculated from the ballistocardiogram in normal persons[5]; however, in shock the relation was inaccurate. Most of these studies were performed on platforms not conforming to the physical principles cited. Several recent studies have revived this problem using the low frequency displacement ballistocardiogram.[6,7] From a theoretical standpoint these calculations should be more accurate than the earlier studies. However, there is a paucity of data on direct comparisons between stroke volume calculated from the ideal ballistocardiogram, and from reference methods, under the necessary carefully controlled conditions.

Another discouraging approach to the ballistocardiogram was the attempt to diagnose many specific cardiovascular disease states from the abnormal patterns encountered. It became quite obvious to most investigators working in the field that very few disease entities were associated with specific wave contours which would aid in the clinical diagnosis. Thus, the general opinion gradually developed that the ballistocardiogram was an interesting phenomenon but generally useless when applied to the problems of clinical medicine.

Ballistocardiogram as Reflection of Myocardial Function

The purpose of this editorial is to point out that in spite of these discouraging problems, the potential use of the technique in clinical medicine could be exceedingly significant, depending upon the questions asked. It now appears quite clearly that the ballistocardiogram is a very sensitive reflection of myocardial function which is not related to specific disease entities or merely to stroke volume alone.

This concept should have been recognized earlier from the studies of Starr and his co-workers.[8–19] The fact that he was able to generate abnormal patterns in the cadavers by altering the way that blood was injected into the aorta clearly supports this concept. Since Starr's classic work on the ballistocardiogram, there have been several significant studies that support this hypothesis. The first is that of Harrison et al.,[20] who measured in a group of 20 patients the first derivative of pressure rise (dp/dt) in the left ventricle simultaneously with ultra-low frequency ballistocardiograms. A close correlation was found between the amplitude of the IJ wave and the maximal first derivative of the left ventricular pressure pulse. Since the maximal dp/dt of the left ventricle is an index of cardiac function, this relation offers significant evidence that the ballistocardiogram does indeed reflect myocardial function.

The second investigation is that of Jackson et al.[21] in a group of patients with hypertrophic subaortic stenosis. Significant relations between certain ballistocardiographic variables and the ejection fraction, as well as the rate of volume ejected by the left ventricle, were demonstrated, again supporting the concept that the ballistocardiogram reflects myocardial function. Bargeron[22] has also recently demonstrated that severity of aortic ventricular gradients in children with aortic stenosis is highly correlated with ballistocardiographic observations.

Ballistocardiogram in early detection of ischemic heart disease: There have now been 3 very exciting investigations relating to the question of early detection of ischemic heart disease. Starr[23–26] initially observed in a long-term follow-up study of so-called normal subjects that patients with initial abnormal contours died earlier than patients whose ballistocardiogram was normal. Similar results were obtained by the group at Hopkins,[27] and recently Taylor and co-workers[28] have observed confirming results. Thus, an abnormal pattern in the ballistocardiogram appears to be a sensitive predictor of probable early mortality. These studies were performed on ballistocardiographic beds that do not meet the standards cited. Artifactual content of the records could only reduce prognostic sensitivity below that obtainable with the optimal apparatus.

Even though older recording techniques were used, the results cannot be overlooked since 3 independent studies have arrived at the same conclusion. A plausible interpretation of these data is as follows: It is well recognized that coronary atherosclerosis begins in early life, particularly in the male, and tends to progress over the years. Since even minimal coronary artery disease is usually associated with areas of patchy fibrosis in the myocardium, one may assume that those subjects who had abnormal ballistocardiograms at an early age already had sufficient decrease in myocardial func-

tion (undetectable by other means) which altered the pattern of the record. Therefore, it can be reasonably concluded that ballistocardiography may very well be the best and most reliable technique for recognizing incipient heart disease or the presence of early changes in myocardial function due to minimal ischemia.

In summary, it would appear that the approach to the study of the ballistocardiogram in general has been in the wrong direction and that its greatest usefulness lies in early detection of heart disease and in evaluating myocardial *functional* abnormalities. Techniques are now available for quantifying myocardial function more precisely, such as the use of the ejection fraction, left ventricular dp/dt, and instantaneous aortic root blood flow in patients. Other indexes of function can be determined by quantitative angiocardiography, and a new look at ballistocardiography should and undoubtedly will be undertaken.

With the present emphasis on early detection of heart disease, we may well have overlooked the most sensitive method available, and one that is easy to apply.

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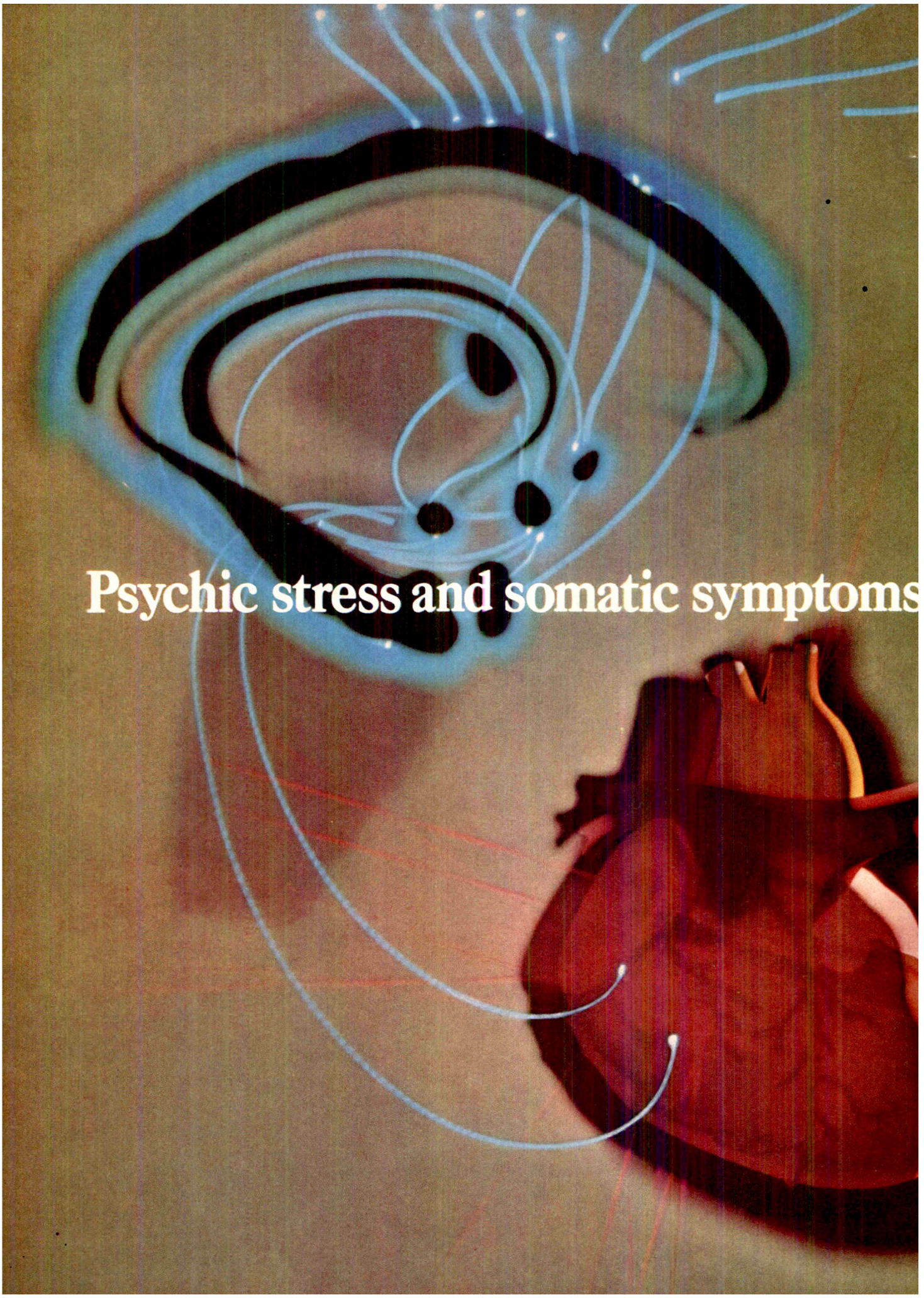
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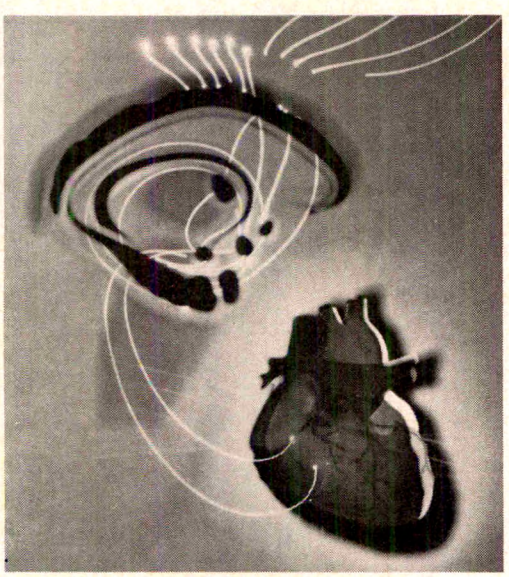

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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation, or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states; 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose™ packages of 1000.

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*patent pending

1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

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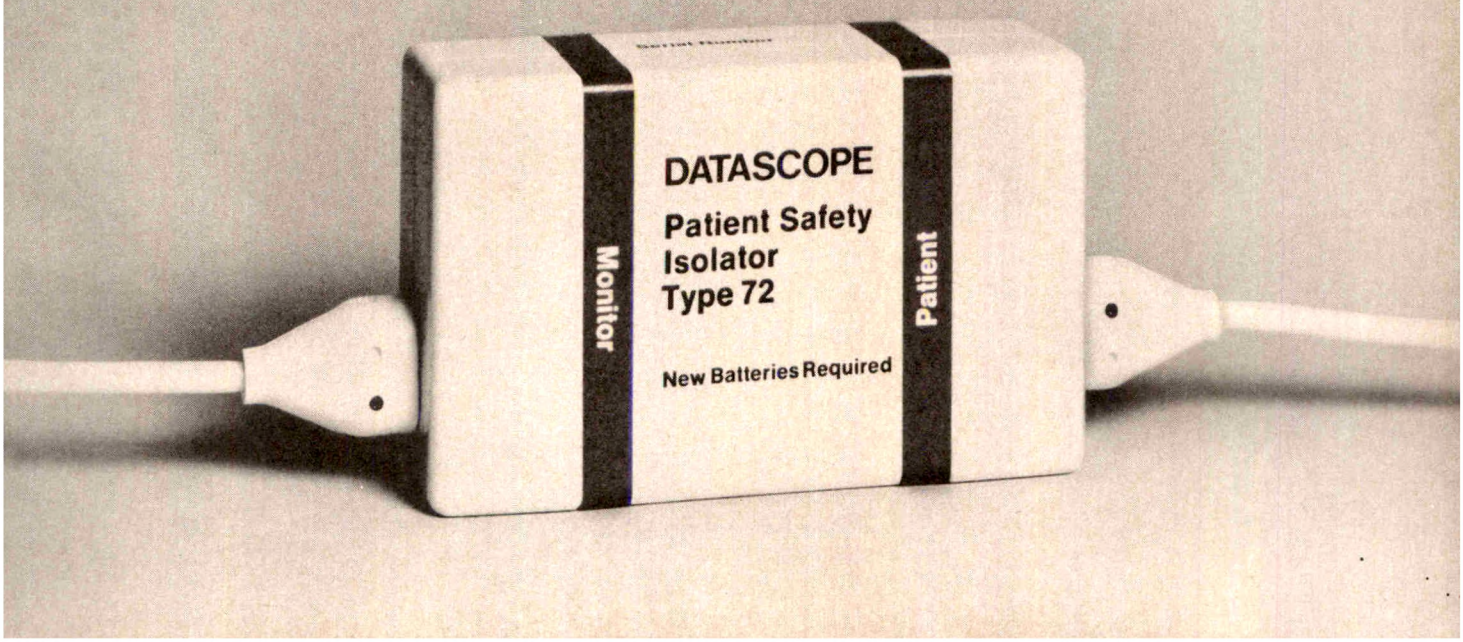

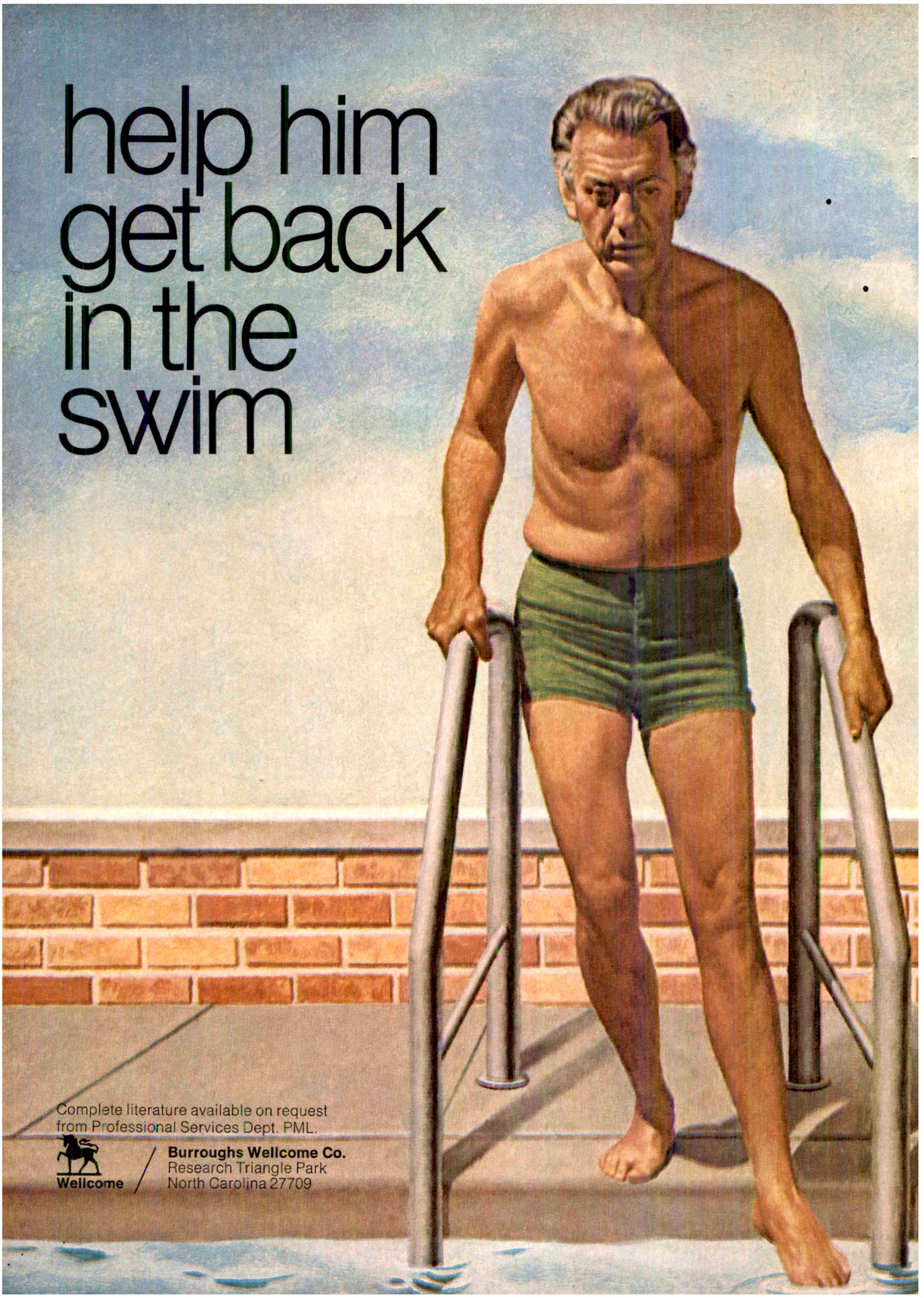
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- improves exercise tolerance
- relieves anginal pain
- reduces nitroglycerin intake
- has longer therapeutic effect than nitroglycerin (*up to 4 hours*)

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PENTAERYTHRITYL TETRANITRATE (PETN)

$O_2N\text{-}O\text{-}CH_2$, $O_2N\text{-}O\text{-}CH_2$ > C < $CH_2\text{-}O\text{-}NO_2$, $CH_2\text{-}O\text{-}NO_2$

Indications: For the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

Precaution: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

Side effects: No serious side effects have been reported. In sublingual therapy, a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound. Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

Supplied: 10 mg. Tablets (scored). Also available in 5 mg. and 15 mg. scored tablets in addition to Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital Tablets (scored).

10 mg. q.i.d. oral or
5 mg. q.i.d. sublingual
suggested starting regimen

improves exercise tolerance in angina pectoris patients

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The good-tasting way to treat hypokalemias induced by thiazide diuretics and other drugs...

Here, at last, is a potassium chloride supplement that just doesn't taste like one! The mixed fruit flavor of new K-Lyte/Cl is truly refreshing. Now, K-Lyte/Cl offers your patients all of the therapeutic advantages you expect from a potassium chloride supplement. And you can be sure that your patients will take the K-Lyte/Cl you prescribe—all in good taste.

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When extra chloride is not desired, original effervescent K-Lyte is unsurpassed in flavor, effective and safe in short- or long-term potassium supplementation. There is little chance of taste fatigue from K-Lyte with two delicious, effervescent flavors to alternate...fresh-tasting orange and sparkling lime.

K-Lyte® Each effervescent tablet in solution supplies 25 mEq. potassium as bicarbonate and citrate

K-Lyte®/Cl Each dose of powder in solution supplies 25 mEq. potassium chloride

Each tablet or dose must be completely dissolved before taking.

Indications: K-Lyte and K-Lyte/Cl are oral potassium supplements for therapy or prophylaxis of potassium deficiency. Particularly useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses. **Contraindications:** Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause. **Warnings and Precautions:** Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water. K-Lyte/Cl contains 4.9 grams (20 calories) of sucrose per dose which should be considered for patients with restriction of caloric intake. **Adverse Reactions:** Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts. **Dosage and Administration:** Adults: 1 tablet or dose *completely dissolved*, 2 to 4 times daily, depending upon the requirements of the patient: K-Lyte: 1 tablet (25 mEq. potassium) in *3 to 4 ounces of cold or ice water;* K-Lyte/Cl: 1 dose (25 mEq. potassium chloride) in *6 ounces of cold or ice water.* The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: *It is suggested that these products be taken with meals and sipped slowly over a 5-10 minute period.* **How Supplied:** K-Lyte: Effervescent tablets—boxes of 30 and 250 (orange or lime flavors). K-Lyte/Cl: Powder, cans of 30 measured doses with scoop (fruit-punch flavor). ℞

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If you'd like complete details about the Physio-Control In Vivo Oximeter, write: Physio-Control Corporation, 2607 Second Avenue, Seattle, Wash. 98121. Telephone (206) 624-4824.

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He wakes up alert and ready to face the demands of the day (Quāālude patients usually awaken easily and without evidence of "hangover")... because he slept well all night (Quāālude usually helps produce 6 to 8 hours of restful sleep)... and he didn't have to lie awake for a long period of time before he went to sleep (Quāālude can induce sleep in 10 to 30 minutes). Now the physician has one less tired, sleepy and apprehensive patient to contend with.

Non-barbiturate Quāālude-300 is chemically unrelated to other sedative-hypnotics. Its therapeutic value has been established in controlled clinical studies and by wide usage of methaqualone throughout the world.

Side effects reported have been mild, transient, and have often proved to be statistically insignificant when compared to placebo effects. (See brief summary on last page of advertisement.)

For these reasons, maybe the prescribing physician sleeps a little better, too.

a non-barbiturate

Quāālude®-300
(methaqualone) 300 mg. tablets

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

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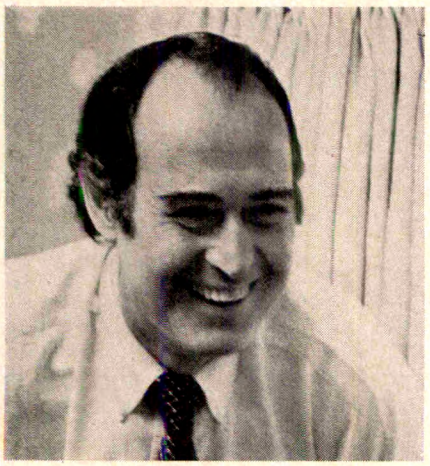
For additional prescribing information, please turn page.

A good morning after a sleep-through night



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sleep usually within 10-30 minutes
sleep duration—6-8 hours
the awakening—pleasantly alert—
usually no "hung-over" feeling

Quāālude®-300
300 mg. tablets
(methaqualone) a non-barbiturate

Brief Summary
of Prescribing Information

Indications:
Sleep. Daytime sedation.

Usual Adult Dose:
For sleep, 150-300 mg. at bedtime. For patients previously on other hypnotics, 300 mg. for five to seven nights. *For sedation,* 75 mg. t.i.d. or q.i.d. Not recommended in children. Dosage should be individualized for aged, debilitated or highly agitated patients.

Overdosage:
Acute overdosage may result in delirium and coma, with restlessness and hypertonia, progressing to convulsions. Evacuate gastric contents, maintain adequate ventilation and support blood pressure, if necessary. Dialysis may be helpful. Analeptics are contraindicated. Succinylcholine accompanied by assisted respiration has been proposed for prolonged convulsions. Overdoses of methaqualone appear to be less often associated with cardiac or respiratory depression than are overdoses of oral barbiturates, but shock and respiratory arrest may occasionally occur.

Contraindications:
Contraindicated in women who are or may become pregnant; or patients with known hypersensitivity.

Warnings:
Take hypnotic dose only at bedtime. Not recommended in children. Warn patient on Quāālude against driving a car or operating dangerous machinery. Care needed when administered with other sedative, analgesic or psychotropic drugs or alcohol because of possible additive effects. Pending longer clinical experience, Quāālude should not be used continuously for periods exceeding three months. *Psychological dependence* occasionally occurs. *Physical dependence* rarely reported. However, caution needed with addiction-prone patients.

Precautions:
Use with caution and prescribe small quantities in patients with anxiety states where impending depression or suicidal tendencies exist. Give in reduced doses, if at all, in patients with impaired hepatic function.

Adverse Reactions:
Neuropsychiatric: headache, hangover, fatigue, dizziness, torpor, transient paresthesia of the extremities. An occasional patient has experienced restlessness or anxiety. *Hematologic:* aplastic anemia possibly related to methaqualone has been very rarely reported. *Gastrointestinal:* dry mouth, anorexia, nausea, emesis, epigastric discomfort, diarrhea. *Dermatologic:* diaphoresis, bromhidrosis, exanthema. Urticaria has been particularly well documented.

Supplied:
Quāālude-150 (150 mg. white, scored tablets). Quāālude-300 (300 mg. white, scored tablets).

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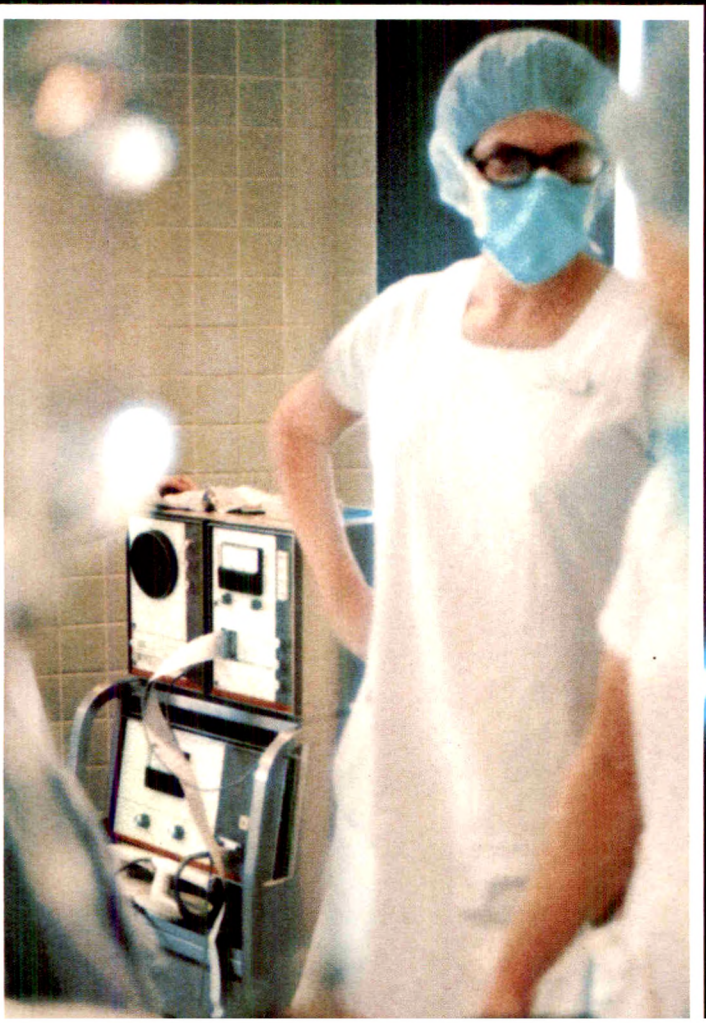

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Book Reviews

Atlas of Nuclear Medicine, Volume 2, Lung and Heart, by Frank H. DeLand, MD and Henry N. Wagner, Jr., MD. Philadelphia, W. B. Saunders, 284 pages, $20.

The rapidity with which this book can be scanned is no indication of the amount of information that can be gleaned from it. The format is outstanding. The quality of the scan reproductions is excellent, and the brief interpretations are more than adequate to explain the illustrative material.

The book is divided into two sections: The first section, covering the lung, makes up three quarters of the book; the final quarter is concerned with the heart. After a brief but adequate section to explain pulmonary segmental anatomy in relation to the perfusion lung scan, illustrative cases are presented to demonstrate normal variants, pulmonary embolization, pulmonary hypertension and infectious and neoplastic diseases of the lung. Each case presentation includes a brief clinical history, a diagnosis prior to scanning, the interpretation of the scan and the subsequent course of the patient. Scans and radiographs are illustrated for each case. For many cases, line drawings of the segmental anatomy with the abnormal segments indicated are included. These line drawings are most helpful to the reader's understanding of the interpretation. In two brief pages, the diagnosis of pulmonary embolization by means of lung scanning and the relationships between the scan and the pulmonary arteriogram are well explained. The average reader will learn a great deal about the usefulness of lung scanning in diseases other than pulmonary embolization in the second half of this first section. The second section indicates the usefulness of blood pool scanning and nuclear angiography in the evaluation of congenital heart disease, pericardial effusion and mediastinal masses in relation to the great vessels.

There are some minor difficulties. At times, a case is presented on several consecutive pages, and it is difficult to compare scans from 1 page to the next. Occasionally, the quality of the reproductions of the chest radiographs is not entirely adequate. On page 221, two of the scans are reversed. Unfortunately, only one page in the lung section is devoted to xenon imaging. The latter represents a rapidly enlarging field of interest in nuclear medicine, and it might have been most helpful to expand this brief section. Moreover, there is no discussion of the combination of perfusion scanning and inhalation scanning in the diagnosis of pulmonary embolization.

This Atlas will undoubtedly find its way onto the shelf of the practitioner of nuclear medicine. For the cardiologist or internist interested in the usefulness of modern scanning, it will prove most helpful.

DONALD J. PINALS, MD
New Rochelle, New York

Dr. Adams

President's Page: How Many Cardiac Surgical Teams Are Necessary?

As one who has been concerned with the rapid proliferation during the past two decades of cardiac surgical teams throughout the United States, I am greatly interested in the recent report of the Surgery Study Group of the Inter-Society Commission for Heart Disease Resources which appeared in *Circulation* 44:A-221, 1971. This group of surgical experts headed by Dr. J. Gordon Scannell of Boston concerned itself with determining the "optimal resources for cardiac surgery." To my mind, they have made some excellent recommendations.

The Surgery Study Group has emphasized that for optimal cardiac surgical results, the necessary disciplines involved must be fully integrated and broadly based, working together preferably in a general hospital. Experience in England has shown that where cardiac surgical units have developed in areas of low population density, and outside of large centers, they have suffered from geographic and academic isolation. The types, qualifications and numbers of persons necessary for staffing a cardiac facility are clearly documented by the Surgery Study Group. In addition, they have made recommendations on the number, size and kinds of physical facilities necessary for a good cardiac unit, which they stress must be operational 24 hours a day and 7 days a week. Their recommendations include standards for prevention of infection, fire and electrical hazards with emphasis on preventive maintenance.

Perhaps the most startling yet reasonable recommendation of the Study Group concerns the relationship between the adequacy of the case load at a center and the quality of care rendered. It is their opinion that a minimal case load of 4 to 6 open heart operations per week plus a reasonable number of closed heart operations per week is essential for members of the cardiac surgical team to maintain their clinical skills, research interests, motivation and morale. If such standards are applied to the results of a recent survey (cited by the Study Group), only 25 cardiac surgical centers in the U. S. and Canada meet their requirement!

Several recent reports indicate that many if not most of the facilities performing cardiac surgery in the U. S. are underutilized to a degree that raises serious questions about their value. It is my opinion that such underutilization not only is bad for the patient, but also greatly increases the cost of such services to the patient and to the public supporting the facilities. In these days of mounting medical costs, can we afford such underutilization? I believe some centralization of services and cost accounting is indicated now.

FORREST H. ADAMS, MD, FACC
President
American College of Cardiology

Advance Program
Twenty-First Annual Scientific Session
American College of Cardiology
Chicago, March 1–5, 1972

General Information

Every effort has been made to organize the 1972 Annual Meeting in such a way that it provides a productive and worthwhile experience for all in attendance. The program is designed within the framework of a growing concern regarding the need for intensive, systematic and quality educational opportunities related to cardiovascular disease.

Advance Registration

Advance registration is requested and will help avoid delays at the time of the scientific session. Please use the Advance Registration Card enclosed with this program. **Deadline for receipt of Advance Registration in the College office is February 9, 1972.**

Chicago, Illinois, Registration Schedule

General Registration:

Continental Room, Conrad Hilton Hotel

Date	Hours
Tuesday, February 29	5:00 P.M.-9:00 P.M.
Wednesday, March 1	8:00 A.M.-9:00 P.M.

Lower Lobby, Conrad Hilton Hotel

Date	Hours
Thursday, March 2	8:00 A.M.-5:00 P.M.
Friday, March 3	8:00 A.M.-5:00 P.M.
Saturday, March 4	8:00 A.M.-5:00 P.M.
Sunday, March 5	8:00 A.M.-12:00 noon

Ladies Registration: Boulevard Room, Conrad Hilton Hotel

Registration Fee

There is no registration fee for the membership of the American College of Cardiology. Non-member fee is seventy-five dollars. Medical students, interns, residents, fellows, members of the armed services, USPHS and VA, nurses, scientific exhibitors and program participants may attend without fee as guests of the American College of Cardiology.

Luncheon Tickets

Seating is limited at the luncheon panels; therefore, early reservation of luncheon tickets is advisable. The Advance Registration Form provides for the reservation of choice. **Admission to the luncheon panel discussions is by ticket only.**

Cardiac Clinics

Seating is limited at these sessions; hence, early reservation of tickets is recommended. The Advance Registration Form provides for the reservation of a ticket of choice. **Admission to these conferences is by ticket only.**

Clinical Conversations with the Master Teachers

Attendance is limited to small groups to assure informal discussion. **Admission is by ticket only and tickets will become available at the time of opening registration at 5:00 p.m. on Tuesday, February 29.**

Fireside Conferences

Fireside Conferences will be held at the Conrad Hilton Hotel. Tickets are not required for Firesides. Attendance is, however, limited to the seating capacity of the room.

Technical and Scientific Exhibits

More than 250 exhibits will be featured at the 1972 Annual Session. All exhibits will be on display at the Conrad Hilton Hotel. Exhibit hours are:

Date	Hours
Thursday, March 2	8:30 A.M.-5:00 P.M.
Friday, March 3	8:30 A.M.-5:00 P.M.
Saturday, March 4	8:30 A.M.-4:00 P.M.

Chicago Art Institute

By special arrangement, the Chicago Art Institute will be open from 5:30 p.m. to 8:30 p.m. on Friday, March 3 for physicians and wives attending the 21st Annual Scientific Session. Round trip bus transportation will be available from the Conrad Hilton Hotel. **Transportation tickets will be on sale in the ACC registration area.**

Lodging

You are requested to use the special Housing Form printed with this program. Blocks of rooms have been reserved at the hotels listed. **Send your request to the address shown on the Housing Form.** Mailing it to the Hotel or to the College office will unnecessarily delay your reservation.

TUESDAY, FEBRUARY 29

P.M.

5:00 to 9:00 Registration—Continental Room, Conrad Hilton Hotel

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WEDNESDAY, MARCH 1

A.M.

8:00 Registration—Continental Room, Conrad Hilton Hotel

A.M.

9:00 to 12:00 noon

READ AND REMEMBER

Beverly Room, Conrad Hilton Hotel

Coordinator: David L. Schmidt, Kansas City, Mo.

Registration Limited to 50.

Enrollment Fee: $25.00

(Above program to be repeated 2:00-5:00 p.m.)

FORMULATION OF INSTRUCTIONAL OBJECTIVES: A CLINICAL SEMINAR

Williford C, Conrad Hilton Hotel

Presented by: The American College of Cardiology in cooperation with The Pacific Medical Center, San Francisco, Calif.

Program Directors: John C. Bish, Ed.D., American College of Cardiology, Bethesda, Md.
Rodger Shepherd, M.D., Pacific Medical Center San Francisco, Calif.

P.M.

2:00 Introduction

2:10 **Small Groups: Writing Instructional Objectives**

3:00 **Small Groups: Writing Instructional Objectives/Application of Instructional Objectives**

4:00 **Small Groups: Applying/Sequencing Instructional Objectives**

4:45 **Summary and Evaluation**

5:00 Adjourn

Registration Limited to 25—Advance Registration is required

Enrollment Fee: $10.00 for American College of Cardiology members
$15.00 for non-members

CARDIAC CLINICS

P.M.

1:00 to 1:30 Bus transportation leaves from the South entrance of Conrad Hilton Hotel on East 8th Street for Cardiac Clinics.

2:00 to 5:00 Because of limited seating facilities at several of the participating institutions, admission to these conferences is by ticket only. The Advance Registration Form enclosed with this program provides an opportunity for the reservation of a ticket of choice.

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1. **The Children's Memorial Hospital**
Bigler Auditorium
707 W. Fullerton Avenue
Chicago, Illinois
Chairman: Milton H. Paul, M.D., F.A.C.C., Chicago, Ill.

TOPICS IN PEDIATRIC CARDIOLOGY

P.M.

2:00 **Introduction to the Children's Memorial Hospital: Cardiology Information Retrieval System**—Milton H. Paul, M.D., F.A.C.C., Chicago, Ill.

2:20 **Management of the Atrial Septal Defect-Ventricular Septal Defect Complex in Infancy**—Sara D. Blumenschein, M.D. and Farouk S. Idriss, M.D., Chicago, Ill.

2:40 **Atrial Septal Defect-Patent Ductus Arteriosus Complex**—Roger B. Cole, M.D. and Edward Lawson, M.D., Chicago, Ill.

2:55 **Exercise Studies for Evaluation of Cardiopulmonary Function in Children and Adolescents**—Hans U. Wessel, M.D., Chicago, Ill.

3:20 INTERMISSION

3:30 **Unusual Systemic-Pulmonary Anastomoses for Tetralogy**—Hisashi Nikaidoh, M.D., and Farouk S. Idriss, M.D., Chicago, Ill.

3:45 **Mass Spectrometer Breath by Breath Gas Analysis for Cardiopulmonary Study**—Ronald Stout, Ph.D., Chicago, Ill.

4:05 **Right Ventricular Outflow Tract Morphology: Pathologic-Angiographic Analysis**—Alexander J. Muster, M.D., F.A.C.C., Chicago, Ill.

4:25 **Surgical Management of Aberrant Muscle Bundle Obstruction of the Right Ventricle**—Farouk S. Idriss, M.D., Chicago, Ill.

4:40 **The Pulmonary Vascular Bed in Transposition of the Great Arteries**—Edgar A. Newfeld, M.D., and Milton H. Paul, M.D., F.A.C.C., Chicago, Ill.

5:00 Adjourn

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2. **Cook County Hospital**
Hektoen Institute
617 South Wood Street—1st floor
Chicago, Illinois
Chairman: Rolf M. Gunnar, M.D., F.A.C.C., Chicago, Ill.
Co-Chairman: Robert Miller, M.D., Chicago, Ill.

MYOCARDIAL INFARCTION

P.M.

2:00 **Monitoring Methods**—Henry S. Loeb, M.D., Chicago, Ill.

2:20 **Ventricular Function**—Shahbudin H. Rahimtoola, M.D., F.A.C.C., Chicago, Ill.

WEDNESDAY (continued)

2:40 **Pharmacologic Support**—Rolf M. Gunnar, M.D., F.A.C.C., Chicago, Ill.

3:00 **Assessment of LV Asynergy**—Peter Geis, M.D., Chicago, Ill.

3:10 INTERMISSION

BILATERAL BUNDLE BRANCH BLOCK

3:30 **Pathology**—Maurice Lev, M.D., F.A.C.C., Chicago, Ill.

4:00 **Electrophysiology**—Kenneth M. Rosen, M.D., F.A.C.C., Chicago, Ill.

4:30 **Right Ventricular Outflow Obstruction: Diagnostic and Surgical Problems**—Robert Miller, M.D., and Constantine J. Tatooles, M.D., F.A.C.C., Chicago, Ill.

5:00 **Surgery in the Neonate**—Constantine J. Tatooles, M.D., F.A.C.C., Chicago, Ill.

5:20 Adjourn

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3. **Loyola University Medical Center**
Lower Level Amphitheater—Room 0708
2160 South 1st Avenue
Maywood, Illinois

Chairman: John R. Tobin, Jr., M.D., F.A.C.C., Chicago, Ill.

Co-Chairmen: Rimgaudas Nemickas, M.D., Chicago, Ill.
Patrick J. Scanlon, M.D., Chicago, Ill.

THE MANAGEMENT OF INTERMEDIATE CORONARY SYNDROME

P.M.

2:00 **Introduction**—John R. Tobin, Jr., M.D., F.A.C.C., Chicago, Ill.

2:15 **Clinical Diagnosis**—John F. Moran, M.D., Chicago, Ill.

2:30 **Medical Therapy**—James V. Talano, M.D., Chicago, Ill.

2:45 **Prognosis**—Patrick J. Scanlon, M.D., Chicago, Ill.

3:00 **Coronary Arteriography**—Rimgaudas Nemickas, M.D., Chicago, Ill.

3:15 INTERMISSION

3:30 **Surgical Indications**—Constantine J. Tatooles, M.D., F.A.C.C., Chicago, Ill.

3:45 **Surgical Procedures and Results**—Roque Pifarre, M.D., Chicago, Ill.

4:00 **Overview of Emergency Direct Myocardial Revascularization**—William C. Sheldon, M.D., F.A.C.C., Chicago, Ill.

4:30 Question and Answer Period

5:00 Adjourn

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4. **Northwestern University Hospital**
Offield Auditorium
Passavant Memorial Hospital
303 East Superior Street
Chicago, Illinois

Chairman: Martin Brandfonbrener, M.D., Chicago, Ill.

Co-Chairman: Oglesby Paul, M.D., F.A.C.C., Chicago, Ill.

CORONARY DISEASE

P.M.

2:00 **Epidemology of Coronary Disease**—Oglesby Paul, M.D., F.A.C.C., Chicago, Ill.

2:20 **Physiology of Occlusion**—William P. McKeever, M.D., F.A.C.C., Chicago, Ill.

2:40 **Coronary Arteriograms**—Sheridan N. Meyers, M.D., and Frank Faksena, M.D., Chicago, Ill.

3:00 **Coronary Unit Record Keeping**—Richard Davison, M.D., Chicago, Ill.

3:20 **Anticoagulant and Coronary Disease**—George Kroll, M.D., F.A.C.C., Chicago, Ill.

3:40 Question and Answer Period

4:05 Adjourn

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5. **Mercy Hospital and Medical Center**
Rooms 203 and 204
Stevenson Expressway at King Drive
Chicago, Illinois

Chairman: H. Dizadji, M.D., F.A.C.C., Chicago, Ill.

SELECTED TOPICS ON MYOCARDIAL INFARCTION AND CORONARY ARTERY VENOUS BY-PASS

P.M.

2:00 Welcome—W. Cernock, M.D., Chicago, Ill.

2:05 **Myocardial Infarction and Hemiblocks**—Agustin Castellanos, Jr., M.D., F.A.C.C., Miami, Fla.

2:30 **Factors Affecting Mortality from Myocardial Infarction During the Acute Phase in the Coronary Care Unit**—H. Dizadji, M.D., F.A.C.C., Chicago, Ill.

2:50 INTERMISSION

3:00 **Factors Affecting Mortality after Coronary Artery Venous By-pass**—T. Hoeksema, M.D., Chicago, Ill.

3:20 **The Use of Propranolol in the Coronary Care Unit**—Herbert Bessinger, M.D., F.A.C.C., Chicago, Ill.

3:40 Panel Discussion and Question and Answer Period

4:05 Adjourn

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6. **Michael Reese Hospital and Medical Center**
Cardiovascular Institute
Rothschild Auditorium, Nurses' Residence
29th Street and Ellis Avenue
Chicago, Illinois

Chairman: Gerald Glick, M.D., Chicago, Ill.

TRENDS IN THE DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR DISEASE

P.M.

2:00 **Treatment of Atrio-ventricular Block in the Patient with Acute Myocardial Infarction**—Richard Langendorf, M.D., F.A.C.C., Chicago, Ill.

2:20 **Arrhythmias in Electrolyte Disturbances**—Alfred Pick, M.D., F.A.C.C., Chicago, Ill.

2:40 **Role of Drugs and Circulatory Assistance in the Treatment of Cardiogenic Shock**—Mario Feola, M.D., Chicago, Ill.

3:00 **Experiences with Coronary Arteriography**—Aaron B. Shaffer, M.D., Chicago, Ill.

3:20 **Role of His Bundle Recordings in the Delineation of Rhythm Disturbances**—Howard C. Cohen, M.D., Chicago, Ill.

WEDNESDAY (continued)

3:40 **Lipoproteins and Atherosclerosis**—Ruth Pick, M.D., Chicago, Ill.

4:05 Adjourn

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7. **Rush Presbyterian-St. Luke's Medical Center**
A. B. Dick Auditorium
1753 West Congress Parkway
Chicago, Illinois

Chairman: Richard A. Carleton, M.D., F.A.C.C., Chicago, Ill.

PATIENT MANAGEMENT AFTER CARDIAC SURGERY

P.M.

2:00 Introduction

2:05 **Myocardial Sequelae of C-P Bypass**—Hassan Najafi, M.D., F.A.C.C., Chicago, Ill.

2:20 **Prevention of Renal Failure**—I. Drummond Rennie, M.D., Chicago, Ill.

2:35 **Respiratory Assistance**—Marshall Goldin, M.D., Chicago, Ill.

2:50 **Analysis of Post-Op Fever**—Stuart Levin, M.D., Chicago, Ill.

3:10 **Diagnosis and Management of Post-Op Bleeding**—Fedor Bachmann, M.D., Chicago, Ill.

3:20 INTERMISSION

3:30 **Management of Arrhythmias**—Stanley Heller, M.D., Chicago, Ill.

3:45 **Management of Low Cardiac Output**—Robert Hauser, M.D., Chicago, Ill.

4:00 Question and Answer Period

5:00 Adjourn

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8. **University of Chicago Clinics and Hospital**
The Center for Continuing Education
Assembly Room
1307 East 60th Street
Chicago, Illinois

Chairman: Leon Resnekov, M.D., F.A.C.C., Chicago, Ill.
Co-Chairman: Harry Fozzard, M.D., Chicago, Ill.

NEW TRENDS IN INVESTIGATION AND TREATMENT

P.M.

2:00 **Cellular and Biochemical Basis of Cardiac Hypertrophy**—Murray Rabinowitz, M.D., F.A.C.C., Chicago, Ill.

2:20 **Quantitive Electron Microscopic Pathology of Heart Muscle**—Ernest Page, M.D., Chicago, Ill.

2:40 **Renin-Angiotensin and Systemaic Hypertension**—Suzanne Oparil, M.D., Chicago, Ill.

3:00 **Diagnosis and Management of Lipoprotein Abnormalities**—Angelo Scanu, M.D., Chicago, Ill.

3:20 INTERMISSION

3:35 **Coronary Care Changing Patterns**—Leon Resnekov, M.D., F.A.C.C., Chicago, Ill.

3:55 **Bilateral Bundle Branch Block**—Roderick Childers, M.D., Chicago, Ill.

4:15 **Computer Recognition of Cardiac Dysrhythmias**—Harry Fozzard, M.D., Chicago, Ill.

4:35 **Assessment of Myocardial Function**—Harold Brooks, M.D., Chicago, Ill.

4:55 Question and Answer Period

5:30 Adjourn

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9. **University of Chicago Wyler Children's Hospital**
Center for Continuing Education
Room 2EF
1307 East 60th Street
Chicago, Illinois

Chairman: René A. Arcilla, M.D., F.A.C.C., Chicago, Ill.
Co-Chairman: Donald E. Cassels, M.D., F.A.C.C., Chicago, Ill.

ADVANCES IN PEDIATRIC CARDIOLOGY

P.M.

2:00 **Deep Hypothermia and Circulatory Arrest in Small Subjects—Clinical and Experimental Studies**—Robert Replogle, M.D., Chung Lin, M.D., Robert Paulissian, M.D., and Harry Lowe, M.D., Chicago, Ill.

2:25 **Myocardial, Biochemical and Ventricular Performance Studies During Open-Heart Surgery**—Anthony Cutilletta, M.D., Robert Replogle, M.D., Chung Lin, M.D., and René A. Arcilla, M.D., F.A.C.C., Chicago, Ill.

2:55 INTERMISSION

3:15 **Multi-Chamber Volume Studies by Angiocardiography in Infants and Children**—René A. Arcilla, M.D., F.A.C.C., Otto Thilenius, M.D., and Klaus Ranniger, M.D., Chicago, Ill.

3:40 **Hemodynamics and Surgical Correction of Rheumatic Mitral Insufficiency in Children**—Otto Thilenius, M.D., Robert Replogle, M.D., and René A. Arcilla, M.D., F.A.C.C., Chicago, Ill.

4:05 Adjourn

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10. **University of Illinois**
College of Pharmacy Building
Room 150-North
833 South Wood
Chicago, Illinois

Chairman: Raymond J. Pietras, M.D., F.A.C.C., Chicago, Ill.

NONINVASIVE TECHNIQUES FOR THE ASSESSMENT OF LEFT VENTRICULAR PERFORMANCE

P.M.

2:00 **Systolic Time Intervals: Determinants and Applications**—Willard Harris, M.D., Chicago, Ill.

2:30 **Normal and Abnormal Responses of Systolic Time Intervals to Exercise**—Jean Maurice Pouget, M.D., F.A.C.C., Chicago, Ill.

3:00 INTERMISSION

3:15 **Heart Tracking: A Noninvasive Method of Measuring Contractility: Experimental and Clinical Evaluation**—Sidney Levitsky, M.D., Chicago, Ill.

3:45 **Instantaneous Changes in Left Ventricular Dimensions Using Epicardial Markers: Correlations with Biplane Cineangiography**—Alois Hastreiter, M.D., F.A.C.C., and Maria E. Serratto, M.D., F.A.C.C., Chicago, Ill.

5:00 Adjourn

WEDNESDAY (continued)

FIRESIDE PANELS

Conrad Hilton Hotel

P.M.

8:30 to 10:00

1. **Understanding Arrhythmias I: The Contribution of Basic Electrophysiology**

   Chairman—Kalman Greenspan, Ph.D., F.A.C.C., Indianapolis, Ind.

   Harry A. Fozzard, M.D., Chicago, Ill.
   Sun H. Lau, M.D., Staten Island, N.Y.
   Donald H. Singer, M.D., F.A.C.C., Chicago, Ill.

2. **Therapeutic Dilemma I: Too Much Digitalis or Too Little?**

   Chairman—Edgar Haber, M.D., Boston, Mass.

   Edward K. Chung, M.D., F.A.C.C., Morgantown, West Va.
   James E. Doherty, M.D., F.A.C.C., Little Rock, Ark.
   Roger W. Jelliffe, M.D., F.A.C.C., Los Angeles, Calif.
   William A. Sodeman, M.D., F.A.C.C., Philadelphia, Pa.

3. **Diagnostic Dilemma I: Constrictive, Restrictive, or Coronary Cardiopathy**

   Chairman—Noble O. Fowler, M.D., F.A.C.C., Cincinnati, Ohio

   Joseph A. Bonanno, M.D., Davis, Calif.
   Oscar Magidson, M.D., F.A.C.C., Los Angeles, Calif.
   Ralph Shabetai, M.D., F.A.C.C., Lexington, Ky.

4. **Auscultation I: Practical Aspects of New Concepts of the Genesis of Heart Sounds**

   Chairman—Joseph K. Perloff, M.D., F.A.C.C., Washington, D.C.

   Aldo A. Luisada, M.D., F.A.C.C., Chicago, Ill.
   Robert O'Rourke, M.D., San Diego, Calif.

5. **Current Concepts in the Classification of Congenital Heart Disease**

   Chairman—Jesse E. Edwards, M.D., F.A.C.C., St. Paul, Minn.

   Maurice Lev, M.D., F.A.C.C., Chicago, Ill.
   L. H. S. Van Mierop, M.D., F.A.C.C., Gainesville, Fla.
   Richard Van Praagh, M.D., F.A.C.C., Boston, Mass.

6. **Biochemical and Mechanical Correlates of Cardiac Contraction**

   Chairman—Edmund H. Sonnenblick, M.D., F.A.C.C., Boston, Mass.

   Marianne Legato, M.D., New York, N.Y.
   C. Lynn Skelton, M.D., Boston, Mass.
   Kenneth Shine, M.D., Los Angeles, Calif.

7. **The Functional Significance of the Coronary Collateral Circulation—Does it Protect?**

   Chairman—Richard J. Bing, M.D., F.A.C.C., Pasadena, Calif.

   Goffredo G. Gensini, M.D., F.A.C.C., Syracuse, N.Y.
   Richard H. Helfant, M.D., Philadelphia, Pa.
   Suzanne B. Knoebel, M.D., F.A.C.C., Indianapolis, Ind.

8. **Newer Concepts in Hyperlipidemic Therapy—Diet, Drugs—Which?**

   Chairman—Robert I. Levy, M.D., F.A.C.C., Bethesda, Md.

   Virgil Brown, M.D., San Diego, Calif.
   William Connor, M.D., Iowa City, Iowa
   Peter T. Kuo, M.D., F.A.C.C., Philadelphia, Pa.

9. **Invasive and Noninvasive Techniques in Evaluating Acute Myocardial Infarction**

   Chairman—Charles E. Rackley, M.D., F.A.C.C., Birmingham, Ala.

   Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.
   Rolf M. Gunnar, M.D., F.A.C.C., Chicago, Ill.
   Robert E. Whalen, M.D., F.A.C.C., Durham, N.C.

10. **Coronary Bypass Graft—Artery or Vein?**

    Chairman—W. Dudley Johnson, M.D., Milwaukee, Wis.

    George E. Green, M.D., New York, N.Y.
    Jerome Harold Kay, M.D., F.A.C.C., Los Angeles, Calif.
    Harold C. Urschel, Jr., M.D., F.A.C.C., Dallas, Tex.

THURSDAY, MARCH 2

A.M.

8:00 Registration—Lower Lobby, Conrad Hilton Hotel

8:30 VISIT EXHIBITS

OPENING PLENARY SESSION

International Ballroom North, Conrad Hilton Hotel

Chairman: Forrest H. Adams, M.D., F.A.C.C., Los Angeles, Calif.

A.M.

9:00 **Presentation of Colors and National Anthem**

Invocation

Introductions—C. Frederick Kittle, M.D., F.A.C.C., Chicago, Ill. (General Chairman, 21st Annual Scientific Session)

Dean T. Mason, M.D., F.A.C.C., Davis, Calif. (Scientific Program Chairman, 21st Annual Scientific Session)

Past Presidents of the College

9:15 **Advances in the Surgical Treatment of Congenital Heart Disease**—John W. Kirklin, M.D., F.A.C.C., Birmingham, Ala.

10:00 INTERMISSION AND VISIT EXHIBITS

SUDDEN DEATH

International Ballroom North, Conrad Hilton Hotel

Chairman: Sylvan L. Weinberg, M.D., F.A.C.C., Dayton, Ohio

A.M.

10:30 **Sudden Death and Hospitalization Delay in Acute Myocardial Infarction**—Sidney Goldstein, M.D., F.A.C.C., William Greene, M.D., and Arthur J. Moss, M.D., F.A.C.C., Rochester, N.Y.

10:45 **Clinical Significance of Ventricular Premature Beats in an Outpatient Population**—Sidney Alexander, M.D., F.A.C.C., Dhiroobhai C. Desai, M.D., and Philip I. Hershberg, M.D., Boston, Mass.

11:00 **Ineffectiveness of Prophylactic Atropine in Decreasing Arrhythmias and Enhancing Survival Following Acute Coronary Artery Occlusion in Conscious Dogs**—Richard B. Karsh, M.D., Michael Orlando, Ph.D., Douglas Norman, B.S., and Stephen E. Epstein, M.D., Bethesda, Md.

THURSDAY (continued)

11:15 **Treatment of Ventricular Arrhythmias Occurring During Acute Coronary Artery Occlusion in Conscious Dogs**—G. David Beiser, M.D., Douglas R. Rosing, M.D., James V. Talano, M.D., Richard B. Karsh, M.D., Martin H. Miller, B.S.E.E., and Stephen E. Epstein, M.D., Bethesda, Md.

11:30 **Prevention of Primary Ventricular Fibrillation in Acute Myocardial Infarction**—Milford G. Wyman, M.D., F.A.C.C., San Pedro, Calif.

11:45 **Sudden Unexpected Death From Coronary Heart Disease: Relationship of Specific Risk Factors and Pathological Findings**—Jack L. Titus, M.D., Herbert A. Oxman, M.D., Fred T. Nobrega, M.D., and Daniel C. Connolly, M.D., F.A.C.C., Rochester, Minn.

CARDIOVASCULAR PHARMACOLOGY

Grand Ballroom, Conrad Hilton Hotel

Chairman: B. L. Martz, M.D., F.A.C.C., Indianapolis, Ind.

A.M.

10:30 **Pharmacokinetics of Intramuscularly Administered Lidocaine**—Martin Sanders, M.D., Arthur H. Hayes, Jr., M.D., and Thomas Killip, M.D., F.A.C.C., New York, N.Y.

10:45 **Comparative Hemodynamic Effects of Procainamide and Lidocaine in Patients with Acute Myocardial Infarction**—Richard R. Miller, M.D., James Lies, M.D., G. Hilliard, M.D., Rashid A. Massumi, M.D., F.A.C.C., Robert F. Zelis, M.D., F.A.C.C., Dean T. Mason, M.D., F.A.C.C., and Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.

11:00 **The Effects of Lidocaine on Refractory Periods in Man**—Mark E. Josephson, M.D., Anthony R. Caracta, M.D., John J. Gallagher, M.D., Sun H. Lau, M.D., and Anthony N. Damato, M.D., Staten Island, N.Y.

11:15 **The Effect of Glucagon on the Ventricular Response in Atrial Fibrillation—A Possible Hazard**—Charles L. Curry, M.D., Joseph E. Hinds, M.D., Ph.D., and Edward W. Hawthorne, M.D., Ph.D., F.A.C.C., Washington, D.C.

11:30 **Effects of Acetylcholine on His-Purkinje Automaticity and Conduction**—John C. Bailey, M.D., Kalman Greenspan, Ph.D., F.A.C.C., Marcelo V. Elizari, M.D., Gary J. Anderson, M.D., John A. Giddings, M.D., and Charles Fisch, M.D., F.A.C.C., Indianpolis, Ind.

11:45 **Potassium and Accelerated Purkinje Conduction**—Gary J. Anderson, M.D., Kalman Greenspan, Ph.D., F.A.C.C., John C. Bailey, M.D., and Charles Fisch, M.D., F.A.C.C., Indianapolis, Ind.

ELECTROPHYSIOLOGY

Continental Room, Conrad Hilton Hotel

Chairman: J. Thomas Bigger, Jr., M.D., F.A.C.C., New York, N.Y.

A.M.

10:30 **Protective Zone for Ventricular Fibrillation**—Marshall Wolf, M.D., Edwards Seroppian, M.D., F.A.C.C., Bernard Lown, M.D., F.A.C.C., John Temte, M.D., Ph.D., Arthur Garfein, M.S.E.E., and R. Verrier, Ph.D., Boston, Mass.

10:45 **Electrophysiological Correlates of Aberrancy in Diseased Hearts**—Donald H. Singer, M.D., F.A.C.C., Robert E. Ten Eick, Ph.D., and Ramalingaier Parameswaran, Chicago, Ill.

11:00 **Supernormality in the Human Heart**—Rashid A. Massumi, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., Z. Vera M.D., Richard R. Miller, M.D., Antone F. Salel, M.D., Gungor E. Ertem, M.D., F.A.C.C., and Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

11:15 **The Mechanism of Activation of the Canine Endocardium**—Robert J. Myerburg, M.D., Kristina Nilsson, and Henry Gelband, M.D., Miami, Fla.

11:30 **The Normal Blood Supply to the His Bundle and Proximal Bundle and Proximal Bundle Branches**—Richard J. Frink, M.D., and Thomas N. James, M.D., F.A.C.C., Birmingham, Ala.

11:45 **Bundle of His Electrograms: Fact or "artiFACT"**—E. Neil Moore, D.V.M., Ph.D., F.A.C.C., J. F. Spear, Ph.D., and J. Melbin, V.M.D., Ph.D., Philadelphia, Pa.

CONGENITAL HEART DISEASE

International Ballroom South, Conrad Hilton Hotel

Chairman: Arthur J. Moss, M.D., F.A.C.C., Los Angeles, Calif.

A.M.

10:30 **Spontaneous Closure of Small Ventricular Defects. Probability Rates in the First Five Years of Life**—Bruce Alpert, B.A., and Richard D. Rowe, M.D., Baltimore, Md.

10:45 **Diminution and Closure of Large Ventricular Septal Defects After Pulmonary Artery Banding**—Zoltan G. Mesko, M.D., Jimmy E. Jones, M.D., and Alexander S. Nadas, M.D., Boston, Mass.

11:00 **Thirty-two Cases of Interventricular Septal Defect in Aortic Insufficiency: Clinical, Hemodynamic and Surgical Features**—Stephen P. Glasser, M.D., Melvin D. Cheitlin, M.D., F.A.C.C., Richard J. McCarty, M.D., F.A.C.C., John H. Haas, M.D., Robert J. Hall, M.D., F.A.C.C., and Charles E. Mullins, M.D., Washington, D.C., San Francisco, Calif., El Paso, Tex., and Tacoma, Wash.

11:15 **Syndrome of Ventricular Septal Defect with Aortic Insufficiency**—Lucy F. Parisi, M.D., Alys M. Holden, M.D., William H. Plauth, M.D., and Alexander S. Nadas, M.D., Boston, Mass.

11:30 **Scimitar Syndrome with Anatomic Variations**—Mehdy Behdad, M.D., and Gordon M. Folger, Jr., M.D., F.A.C.C., Augusta, Ga.

11:45 **The Association of Vascular Ring and Unusual Facial Appearance**—Kimio Yashiro, M.D., Mitsuru Osano, M.D., Tadao Oikawa, M.D., Atsutoshi Tsuji, M.D., Toru Ota, M.D., and Kazuaki Kato, M.D., Tokyo, Japan

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SELF-ASSESSMENT CLASSROOM

Bel Air Room, Conrad Hilton Hotel

A.M.

9:00 to 5:00 p.m.

The 1972 Self-Assessment classroom will focus on the Clinical Interpretation of Electrocardiograms. Primary emphasis will be placed on **mechanisms** of arrhythmias and QRS abnormalities. The correct answer will be given after each question. The answer sheets will be collected—anonymously—and an overall distribution of answers (and the correct answer) will be determined. This will permit the physician-learner to compare his responses to those of others. Selected questions will be discussed later in the ACCESS® audio journal.

THURSDAY (continued)

LUNCHEON PANELS

Conrad Hilton and Sheraton Blackstone Hotels

P.M.
12:00 to 1:30

1. **New Concepts in Catheterization Techniques of Children and Neonates**

   Chairman—Arthur J. Moss, M.D., F.A.C.C., Los Angeles, Calif.

   Rene A. Arcilla, M.D., F.A.C.C., Chicago, Ill.
   Herbert D. Ruttenberg, M.D., F.A.C.C., Salt Lake City, Utah
   Masato Takahashi, M.D., F.A.C.C., Los Angeles, Calif.

2. **The Surgical Therapy of Cardiogenic Shock—When to Intervene?**

   Chairman—Elliot Rapaport, M.D., San Francisco, Calif.

   Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.
   Mortimer Buckley, M.D., Boston, Mass.
   William W. Parmley, M.D., F.A.C.C., Encino, Calif.

3. **The Management of Aneurysms (Dissecting and Otherwise)**

   Chairman—C. Frederick Kittle, M.D., F.A.C.C., Chicago, Ill.

   Arthur C. Beall, Jr., M.D., F.A.C.C., Houston, Tex.
   Roger F. Palmer, M.D., Encino, Calif.
   Myron W. Wheat, Jr., M.D., F.A.C.C., Gainesville, Fla.

4. **Critical Evaluation of Invasive Techniques in the CCU**

   Chairman—H. J. C. Swan, M.D., F.A.C.C., Los Angeles, Calif.

   Peter L. Frommer, M.D., F.A.C.C., Bethesda, Md.
   Bernard Lown, M.D., F.A.C.C., Boston, Mass.
   Max Harry Weil, M.D., F.A.C.C., Los Angeles, Calif.

5. **Atypical Angina (Angina with Normal Coronary Arteriograms)**

   Chairman—William Likoff, M.D., F.A.C.C., Philadelphia, Pa.

   D. Luke Glancy, M.D., F.A.C.C., Bethesda, Md.
   Harvey G. Kemp, Jr., M.D., F.A.C.C., New York, N.Y.
   F. Mason Sones, Jr., M.D., F.A.C.C., Cleveland, Ohio

6. **Office Evaluation of Ventricular Function by Sequential Graphic Techniques**

   Chairman—Arnold M. Weissler, M.D., F.A.C.C., Detroit, Mich.

   Ernest Craige, M.D., F.A.C.C., Chapel Hill, N.C.
   Harvey Feigenbaum, M.D., F.A.C.C., Indianapolis, Ind.
   Willard S. Harris, M.D., Chicago, Ill.

7. **The Spectrum of Newer Antiarrhythmic Agents**

   Chairman—Leonard S. Dreifus, M.D., F.A.C.C., Philadelphia, Pa.

   Marvin I. Dunn, M.D., F.A.C.C., Kansas City, Kan.
   Robert J. Luchi, M.D., F.A.C.C., Iowa City, Iowa
   Park W. Willis, III, M.D., F.A.C.C., Ann Arbor, Mich.

8. **Medical vs. Surgical Therapy of Secondary Forms of Hypertension**

   Chairman—Roger B. Hickler, M.D., F.A.C.C., Worcester, Mass.

   Harriet P. Dustan, M.D., Cleveland, Ohio
   Edward D. Frolich, M.D., F.A.C.C., Oklahoma City, Okla.
   Gaddo Onesti, M.D., Philadelphia, Pa.

9. **Alcohol and the Heart**

   Chairman—George E. Burch, M.D., F.A.C.C., New Orleans, La.

   Jere H. Mitchell, M.D., F.A.C.C., Dallas, Tex.
   Timothy J. Regan, M.D., Newark, N.J.
   David H. Spodick, M.D., F.A.C.C., Boston, Mass.

1:30 VISIT EXHIBITS

SURGERY AND CORONARY ARTERY DISEASE

International Ballroom North, Conrad Hilton Hotel

Chairman: W. Gerald Austen, M.D., F.A.C.C., Boston, Mass.

Co-Chairman: C. Frederick Kittle, M.D., F.A.C.C., Chicago, Ill.

P.M.

2:00 **The Medical Assessment of the Coronary Artery Patient: Who Should Have Arteriography?**—Henry D. McIntosh, M.D., F.A.C.C., Houston, Tex.

2:15 **Cardiac Catheterization and Angiographic Diagnosis—The Sones Technique**—F. Mason Sones, Jr., M.D., F.A.C.C., Cleveland, Ohio

2:30 **Cardiac Catheterization and Angiographic Diagnosis—The Judkins Technique**—Melvin P. Judkins, M.D., F.A.C.C., Loma Linda, Calif.

2:45 **Selection of Patients for Surgery**—Richard S. Ross, M.D., F.A.C.C., Baltimore, Md.

3:00 **Coronary Artery Surgery and the Treatment of Angina**—W. Dudley Johnson, M.D., Milwaukee, Wis.

3:15 **Coronary Artery Surgery and the Treatment of Congestive Heart Failure**—Eldred D. Mundth, M.D., Boston, Mass.

3:30 INTERMISSION AND VISIT EXHIBITS

4:00 **Coronary Artery Surgery for Impending or Actual Acute Myocardial Infarction**—Roque Pifarre, M.D., Hines, Ill.

4:15 **Surgery for the Mechnical Complications of Myocardial Infarction—Mitral Valve Surgery, Repair of Ventricular Septal Defects, and Infarctectomy**—Jerome H. Kay, M.D., F.A.C.C., Los Angeles, Calif.

4:30 **The Late Results in Coronary Artery Surgery**—John C. Manley, M.D., F.A.C.C., Milwaukee, Wis.

4:45 **Panel Discussion**—Drs. Johnson, Judkins, Kay, McIntosh, Manley, Mundth, Pifarre, Ross and Sones; Dr. Austen, moderator.

5:30 Adjourn

CORE CURRICULUM IN CLINICAL CARDIOLOGY

Grand Ballroom, Conrad Hilton Hotel

The purpose of the Core Curriculum in Clinical Cardiology is to present up-to-date information which has contributed to our understanding of pathophysiology, diagnosis and management of patients with heart disease. With this in mind the individual papers will avoid specific ex-

THURSDAY (continued)

perimental designs or data, except when important to the over-all broad, "synthesizing" summary of the presently available information.

Chairman: William Likoff, M.D., F.A.C.C., Philadelphia, Pa.

CARDIAC FUNCTION AND MECHANISMS

P.M.

2:00 **Cardiac Pathology and the Clinical Cardiologist**—William C. Roberts, M.D., F.A.C.C., Bethesda, Md.

2:45 **Autonomic Nervous System and the Circulation**—Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

3:30 INTERMISSION AND VISIT EXHIBITS

4:00 **Electrophysiology of Arrhythmias**—Charles Fisch, M.D., F.A.C.C., Indianapolis, Ind.

4:45 **The Heart as a Pump**—Harold T. Dodge, M.D., F.A.C.C., Seattle, Wash.

CLINICAL CONVERSATIONS WITH THE MASTER TEACHERS

Attendance is limited to fifteen physicians per teacher and **admission is by ticket only.** Tickets will be available at the ACC registration area in the Conrad Hilton Hotel beginning at 5:00 p.m. on Tuesday, February 29.

Parlors 534, 545, 546, 547, Conrad Hilton Hotel

P.M.

2:00-3:00—Group I

4:00-5:00—Group II

Master Teachers: William B. Abrams, M.D., F.A.C.C., New York, N.Y.

Alberto Benchimol, M.D., F.A.C.C., Phoenix, Ariz.

Jesse E. Edwards, M.D., F.A.C.C., St. Paul, Minn.

Charles K. Friedberg, M.D., F.A.C.C., New York, N.Y.

CONGENITAL HEART DISEASE

Continental Room, Conrad Hilton Hotel

Chairman: Samuel Kaplan, M.D., F.A.C.C., Cincinnati, Ohio

P.M.

2:00 **New England Regional Infant Cardiac Program**—Donald C. Fyler, M.D., Lucy F. Parisi, M.D., Norman S. Talner, M.D., F.A.C.C., New Haven, Conn.

2:15 **The Diagnosis of Aortic Atresia by Echocardiography**—Richard A. Meyer, M.D., David C. Schwartz, M.D., F.A.C.C., and Samuel Kaplan, M.D., F.A.C.C., Cincinnati, Ohio

2:30 **The Transition from Double Outlet Right Ventricle to Complete Transposition-Pathologic Study**—D. A. Goor, M.D., and Jesse E. Edwards, M.D., F.A.C.C., St. Paul, Minn.

2:45 **Factors Influencing Intercirculatory Mixing in Complete Transposition of the Great Arteries**—Douglas D. Mair, M.D., Donald G. Ritter, M.D., F.A.C.C., Rochester, Minn.

3:00 **Dysrhythmias and Conduction Defects with Pathological Study of the Sino-Atrial Node after Mustard's Operation for Transposition of the Great Arteries**—Galal El-Said, M.D., Harvey S. Rosenberg, M.D., Charles E. Mullins, M.D., Grady L. Hallman, M.D., F.A.C.C., Denton A. Cooley, M.D., F.A.C.C., and Dan G. McNamara, M.D., F.A.C.C., Houston, Tex.

3:15 **Congenital Polyvalvular Disease**—Saroja Bharati, M.D., and Maurice Lev, M.D., F.A.C.C., Chicago, Ill.

3:30 INTERMISSION AND VISIT EXHIBITS

Chairman: Dan G. McNamara, M.D., F.A.C.C., Houston, Tex.

4:00 **Late Systolic Mitral Regurgitation in Children**—David C. Schwartz, M.D., F.A.C.C., Samuel Kaplan, M.D., F.A.C.C., and Richard A. Meyer, M.D., Cincinnati, Ohio

4:15 **Systolic Intervals in Children with Normal and Diseased Hearts**—Masato Takahashi, M.D., F.A.C.C., and David L. Moritz, B.S., Los Angeles, Calif.

4:30 **Mechanism of Cardiac Failure in Experimental Patent Ductus Arteriosus**—William R. Vincent, M.D., James R. Sakamoto, B.S., and Gerald D. Buckberg, M.D., Los Angeles, Calif.

4:45 **The Effect of Variation in Arterial Oxygen Tension on Fetal Circulation**—Bijan Siassi, M.D., Irwin Tessler, M.D., Paul Y. K. Wu, M.D., Houchang Modanlou, M.D., and Raymond Li, M.D., Los Angeles, Calif.

5:00 **Defective Platelet Aggregation in Congenital Heart Disease**—Harold M. Maurer, M.D., Carolyn M. McCue, M.D., F.A.C.C., J. Caul, B.S., and William J. S. Still, M.D., Richmond, Va.

5:15 **The Collateral Venous Circulation after Glenn Anastomosis**—Robert B. Karp, M.D., Benigno Soto, M.D., F.A.C.C., Lionel M. Bargeron, M.D., F.A.C.C., and Alberto Barcia, M.D., F.A.C.C., Birmingham, Ala.

CARDIAC MUSCLE SOCIETY

Mayfair Room, Sheraton Blackstone Hotel

Chairman: Edmund H. Sonnenblick, M.D., F.A.C.C., Brookline, Mass.

V_{MAX}: FACT OR FANCY

P.M.

2:00 **Contractile Activity of Isolated Cardiac Muscle**—Dirk L. Brutsaert, M.D., Antwerp, Belgium

2:45 **Cardiac Mechanics in the Intact Heart: Experimental Approaches**—John Ross, Jr., M.D., F.A.C.C., San Diego, Calif.

3:30 INTERMISSION AND VISIT EXHIBITS

4:00 **Evaluation of Pediatric Heart Disease**—R. Curtis Ellison, M.D., Boston, Mass.

4:45 **Clinical Studies in Heart Disease: Usefulness and Limitation**—Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

5:30 **Summary**—Edmund H. Sonnenblick, M.D., F.A.C.C., Brookline, Mass.

THURSDAY (continued)

PREMIERE CINE SEMINAR

International Ballroom South, Conrad Hilton Hotel

• First National Showing of Motion Pictures in Cardiovascular Disease

P.M.

3:00 to 5:30

• Film titles to be announced

FIRESIDE PANELS

Conrad Hilton Hotel

P.M.

8:30 to 10:00

1. **Understanding Arrhythmias II: The Contribution of His Electrocardiography**

   Chairman—Rashid A. Massumi, M.D., F.A.C.C., Davis, Calif.

   Agustin Castellanos, Jr., M.D., F.A.C.C., Miami, Fla.
   Anthony N. Damato, M.D., Staten Island, N.Y.
   Richard Langendorf, M.D., F.A.C.C., Chicago, Ill.

2. **Therapeutic Dilemma II: The Unresponsive PVC**

   Chairman—Lawrence S. Cohen, M.D., F.A.C.C., New Haven, Conn.

   Keith E. Cohn, M.D., F.A.C.C., San Francisco, Calif.
   Roman W. DeSanctis, M.D., F.A.C.C., Boston, Mass.
   Michael D. Klein, M.D., F.A.C.C., Boston, Mass.
   Stephen M. Wittenberg, M.D., Buffalo, N.Y.

3. **Diagnostic Dilemma II: Pulmonary Edema, Embolism or Infection**

   Chairman—Arthur A. Sasahara, M.D., F.A.C.C., Boston, Mass.

   Daniel Flamm, Jr., M.D., F.A.C.C., Travis AFB, Calif.
   John H. K. Vogel, M.D., F.A.C.C., Santa Barbara, Calif.
   Paul N. Yu, M.D., F.A.C.C., Rochester, N.Y.

4. **Auscultation II: The Difficult Diagnosis**

   Chairman—W. Proctor Harvey, M.D., F.A.C.C., Washington, D.C.

   Alberto Benchimol, M.D., F.A.C.C., Phoenix, Ariz.
   Bernard L. Segal, M.D., F.A.C.C., Philadelphia, Pa.
   Mark E. Silverman, M.D., F.A.C.C., Atlanta, Ga.

5. **Management of Cyanotic Congenital Heart Disease**

   Chairman—William Rashkind, M.D., Philadelphia, Pa.

   Gerard A. Kaiser, M.D., Miami, Fla.
   Dan G. McNamara, M.D., F.A.C.C., Houston, Tex.
   Milton H. Paul, M.D., F.A.C.C., Chicago, Ill.

6. **Basic Biochemical Defects in Congestive Heart Failure**

   Chairman—Henry Neal Coleman, M.D., Rochester, Minn.

   Norman R. Alpert, M.D., Burlington, Vt.
   Murray Rabinowitz, M.D., F.A.C.C., Chicago, Ill.
   James Scheuer, M.D., F.A.C.C., Pittsburgh, Pa.

7. **Irreversible Shock: The Pulmonary Splanchnic, Intrarenal and Peripheral Circulations**

   Chairman—Jay N. Cohn, M.D., F.A.C.C., Washington, D. C.

   Gerald Glick, M.D., Chicago, Ill.
   Allyn L. Mark, M.D., Iowa City, Iowa
   Herbert S. Shubin, M.D., F.A.C.C., Los Angeles, Calif.

8. **Invasive and Noninvasive Techniques in Evaluating Chronic Coronary Artery Disease**

   Chairman—Harold T. Dodge, M.D., F.A.C.C., Seattle, Wash.

   J. Michael Criley, M.D., F.A.C.C., Torrance, Calif.
   Melvin P. Judkins, M.D., F.A.C.C., Loma Linda, Calif.
   Robert Kraus, M.D., Beverly Hills, Calif.
   Arnold M. Weissler, M.D., F.A.C.C., Detroit, Mich.

9. **The Medical Therapy of Cardiogenic Shock—A Losing Battle?**

   Chairman—Eliot Corday, M.D., F.A.C.C., Los Angeles, Calif.

   Leslie A. Kuhn, M.D., F.A.C.C., New York, N.Y.
   Charles A. Sanders, M.D., Boston, Mass.
   Max Harry Weil, M.D., F.A.C.C., Los Angeles, Calif.
   John F. Williams, Jr., M.D., F.A.C.C., Galveston, Tex.

10. **Are Pacemakers of Value in Acute Myocardial Infarction?**

    Chairman—Simon Dack, M.D., F.A.C.C., New York, N.Y.

    L. Julian Haywood, M.D., F.A.C.C., Los Angeles, Calif.
    Philip Samet, M.D., F.A.C.C., Miami Beach, Fla.
    Arthur Selzer, M.D., F.A.C.C., San Francisco, Calif.

FRIDAY, MARCH 3

A.M.

8:00 Registration—Lower Lobby, Conrad Hilton Hotel

PAUL WOOD REMEMBERED

International Ballroom North, Conrad Hilton Hotel

Chairmen: E. Grey Dimond, M.D., F.A.C.C., Kansas City, Mo. Oscar Magidson, M.D., F.A.C.C., Los Angeles, Calif.

A.M.

9:00 **Introduction**—E. Grey Dimond, M.D., F.A.C.C., Kansas City, Mo.

9:15 **Paul Wood, His Life & Work**—Walter Somerville, M.D., London, England

9:50 **An Appreciation of Mitral Stenosis 1972**—Arthur Selzer, M.D., F.A.C.C., San Francisco, Calif.

10:20 **Coronary Flow in the Anginal Patient. What Can Be Believed?**—Maurice McGregor, M.D., F.A.C.C., Montreal, Can.

10:50 INTERMISSION AND VISIT EXHIBITS

11:15 **What Happens After Cardiac Infarction?**—E. Lawson McDonald, M.D., F.A.C.C., London, England

(Continued in P.M.)

CORE CURRICULUM IN CLINICAL CARDIOLOGY

Grand Ballroom, Conrad Hilton Hotel

FRIDAY (continued)

Chairman: Eliot Corday, M.D., F.A.C.C., Los Angeles, Calif.

CARDIAC FUNCTION AND MECHANISMS

A.M.

8:30 **Sudden Death**—Bernard Lown, M.D., F.A.C.C., Boston, Mass.

9:15 **Noninvasive Assessment of Cardiac Function**—Donald C. Harrison, M.D., F.A.C.C., Stanford, Calif.

10:00 INTERMISSION AND VISIT EXHIBITS

10:30 **Renal Function and the Cardiologist**—Walter M. Kirkendall, M.D., F.A.C.C., Iowa City, Iowa

11:15 **Pulmonary Embolism and Cor Pulmonale**—Walter J. Daly, M.D., F.A.C.C., Indianapolis, Ind.

CORONARY ARTERY DISEASE

Continental Room, Conrad Hilton Hotel

Chairman: Herman K. Hellerstein, M.D., F.A.C.C., Cleveland, Ohio

A.M.

8:30 **Natural History of Severe Proximal Coronary Disease as Defined by Cineaniography. (Two hundred patients, seven year follow up).**—Carl H. Moberg, M.D., Joel S. Webster, M.D., and F. Mason Sones, Jr., M.D., F.A.C.C., Cleveland, Ohio

8:45 **The Evolution of Coronary Arterial Pathology in Patients with Angina Pectoris as Determined by the Coronary Arteriogram**—Demetrios Kimbiris, M.D., Peter Lavine, M.D., Hans Van den Broek, M.D., Moosa Naimi, M.D., and William Likoff, M.D., F.A.C.C., Philadelphia, Pa.

9:00 **The Diffuse Nature of Coronary Arterial Atherosclerosis in Fatal Acute Myocardial Infarction**—William C. Roberts, M.D., F.A.C.C., and L. Maximilian Buja, M.D., Bethesda, Md.

9:15 **Determinants and Functional Significance of the Coronary Collateral Circulation in Patients with Coronary Artery Disease**—Richard R. Miller, M.D., Dean T. Mason, M.D., F.A.C.C., Anthone Salel, M.D., Robert F. Zelis, M.D., F.A.C.C., Rashid A. Massumi, M.D., F.A.C.C., and Ezra Amsterdam, M.D., F.A.C.C., Davis, Calif.

9:30 **Long Term Observations in Patients with Angina and Normal Coronary Arteriograms**—Carl R. Bemiller, M.D., C. J. Pepine, M.D., and A. Rogers, M.D., Philadelphia, Pa.

9:45 **Detection of the Inaudible Murmur of Coronary Stenosis by a Synchronized Sound Averaging Technique**—Leonard Karpman, M.D., John Cage, Emmanuel Furst, Charles M. Hill, Walter E. Berger, M.D., and Keith E. Cohn, M.D., F.A.C.C., San Francisco, Calif., and Stanford, Calif.

10:00 INTERMISSION AND VISIT EXHIBITS

Chairman: Robert W. Oblath, M.D., F.A.C.C., Sherman Oaks, Calif.

10:30 **The Relationship of Anginal Symptoms to Lung Mechanics During Myocardial Ischemia**—Carl J. Pepine, M.D., and Leslie Wiener, M.D., F.A.C.C., Philadelphia, Pa.

10:45 **A Study of the Effect of the Argus Computer System on Treatment Actions in a Coronary Care Unit**—G. Charles Oliver, M.D., F.A.C.C., Floyd M. Nolle, M.S., Alan J. Tiefenbrunn, A.B., and Kenneth W. Clark, B.S., St. Louis, Mo.

11:00 **Salvage of Myocardial Tissue by Coronary Artery Reperfusion Following Acute Coronary Occlusion**—Peter R. Maroko, M.D., William R. Ginks, M.D., Peter Libby, William E. Shell, M.D., Burton E. Sobel, M.D., F.A.C.C., and John Ross, Jr., M.D., F.A.C.C., La Jolla, Calif.

11:15 **Functional Development of the Coronary Collateral Circulation During Acute Myocardial Infarction in the Conscious Dog**—Colin M. Bloor, M.D., F.A.C.C., and Francis C. White, B.S., La Jolla, Calif.

11:30 **Alterations in Renal Vascular Resistance Following Coronary Artery Occlusion in Dogs**—Henry G. Hanley, M.D., Albert E. Raizner, M.D., Thomas V. Inglesby, M.D., and Newman S. Skinner, Jr., M.D., Atlanta, Ga.

11:45 **Occlusive Coronary Disease in the Transplanted Denervated Heart: Assessment by Exercise EKG and Coronary Arteriography**—Anthony F. Graham, M.D., John S. Schroeder, M.D., and Donald C. Harrison, M.D., F.A.C.C., Stanford, Calif.

ELECTROCARDIOGRAPHY

International Ballroom South, Conrad Hilton Hotel

Chairman: Simon Dack, M.D., F.A.C.C., New York, N.Y.

A.M.

8:30 **Prediction of Acute Changes in Left Atrial Hemodynamics from the P Wave**—Paul G. Hugenholtz, M.D., F.A.C.C., J. Heikkila, M.D., and C. V. Nelson, M.D., Rotterdam, Netherlands, and Portland, Maine

8:45 **Usefulness of the Electrocardiogram in Assessment of Ventricular Performance and Comparison with Coronary Arteriography**—Richard R. Miller, M.D., J. Bonanno, M.D., Rashid A. Massumi, M.D., F.A.C.C., Robert F. Zelis, M.D., F.A.C.C., Dean T. Mason, M.D., F.A.C.C., and Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.

9:00 **Heritable Cardiac Conduction Disease: Left Axis Deviation, Right Bundle Branch Block, Complete Heart Block and Early Death**—Stephen F. Schaal, M.D., John F. Seidensticker, M.D., Richard M. Goodman, M.D., and Charles F. Wooley, M.D., Columbus, Ohio

9:15 **Wolf-Parkinson-White Syndrome in the Neonate: Nine Cases Including Two With Intrauterine Defects**—Rumbha V. Bhandhusavee, M.D., Linda R. Walters, M.D., and Jacqueline A. Noonan, M.D., F.A.C.C., Lexington, Ky.

9:30 **Incidence and Nature of Arrhythmias in the Early Hospital Post-Coronary Care Unit Phase of Acute Myocardial Infarction**—L. Vismara, M.D., J. L. Hughes, M.D., J. Bonanno, M.D., Rashid A. Massumi, M.D., F.A.C.C., Robert F. Zelis, M.D., F.A.C.C., Dean T. Mason, M.D., F.A.C.C., and Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.

9:45 **Learned Control of Ventricular Rate in Patients with Atrial Fibrillation**—Eugene R. Bleecker, M.D., and Bernard T. Engle, Ph.D., Baltimore, Md.

10:00 INTERMISSION AND VISIT EXHIBITS

CARDIOVASCULAR PHARMACOLOGY

International Ballroom South, Conrad Hilton Hotel

Chairman: Alfred Soffer, M.D., F.A.C.C., Chicago, Ill.

A.M.

10:30 **Tritiated Digoxin Uptake by the Normal and Hypertrophied Rabbit Myocardium**—Marvin L. Murphy, M.D., F.A.C.C., and James E. Doherty, M.D., F.A.C.C., Little Rock, Ark.

10:45 **The Effects of Ouabain and Diphenylhydantoin on Myocardial Potassium Balance in Man**—J. L. McCans, M.D., Francis J. Brennan, M.D., Miquiel A. Chiong, M.D., Ph.D., John O. Parker, M.D., F.A.C.C., Kingston, Can.

FRIDAY (continued)

11:00 **Correlation of the Antiarrhythmic Effects of Diphenylhydantoin with Digoxin-Induced Changes in Myocardial Contractility, NA^+-K^+ Dependent ATPhase and K^+ Efflux**—Robert E. Goldstein, M.D., Stanley C. Penzotti, Ph.D., Karen S. Kuehl, M.D., Kirk H. Prindle, M.D., Clifford A. Hall, M.D., Elwood O. Titus, Ph.D., and Stephen E. Epstein, M.D., Bethesda, Md.

11:15 **Studies of Cardiac Pharmacology in Intact Animals and Isolated Cardiac Tissues**—Michael R. Rosen, M.D., Henry Gelband, M.D., Vincent P. Butler, Jr., M.D., and Brian F. Hoffman, M.D., New York, N.Y.

11:30 **Nitrous Oxide as an Analgesic in Acute Myocardial Infarction**—Peter L. Thompson, M.B., and Bernard Lown, M.D., F.A.C.C., Boston, Mass.

11:45 **Evidence for the Direct Effects of Adrenergic Drugs on the Cerebral Vascular Bed**—Salvador Lluch, M.D., Charles Reimann, M.D., and Gerald Glick, M.D., Chicago, Ill.

CLINICAL CONVERSATIONS WITH THE MASTER TEACHERS

Attendance is limited to fifteen physicians per teacher and **admission is by ticket only.** Tickets will be available at the ACC registration area in the Conrad Hilton Hotel beginning at 5:00 p.m. on Tuesday, February 29, 1972.

Parlors 534, 545, 546, 547, Conrad Hilton Hotel

A.M.

9:00-10:00—Group I

11:00-12:00—Group II

Master Teachers: Eugene Braunwald, M.D., F.A.C.C., San Diego, Calif.
Thomas N. James, M.D., F.A.C.C., Birmingham, Ala.
Joseph K. Perloff, M.D., F.A.C.C., Washington, D. C.
Edmund H. Sonnenblick, M.D., F.A.C.C., Brookline, Mass.

SELF-ASSESSMENT CLASSROOM

Bel Air Room, Conrad Hilton Hotel

A.M.

9:00 to 5:00 p.m.

LUNCHEON PANELS

Conrad Hilton and Sheraton Blackstone Hotels

P.M.

12:00 to 1:30

1. **The Treatment of Endocardial Cushion Defects**

   Chairman—Samuel Kaplan, M.D., F.A.C.C., Cincinnati, Ohio

   Mary Allen Engle, M.D., F.A.C.C., New York, N.Y.
   Russell V. Lucas, M.D., Minneapolis, Minn.
   Dwight C. McGoon, M.D., Rochester, Minn.
   Jane Somerville, M.D., London, England

2. **Does the Aorto-Coronary Bypass Graft Alter Prognosis in Coronary Artery Disease?**

   Chairman—Henry D. McIntosh, M.D., F.A.C.C., Houston, Tex.

   Robert L. Reis, M.D., Kansas City, Kan.
   Richard S. Ross, M.D., F.A.C.C., Baltimore, Md.
   Albert Starr, M.D., F.A.C.C., Portland, Ore.

3. **Valve Replacement Revisited: When To, What Kind, Prognosis?**

   Chairman—John Ross, Jr., M.D., F.A.C.C., San Diego, Calif.

   William Angell, M.D., San Jose, Calif.
   Nina S. Braunwald, M.D., F.A.C.C., San Diego, Calif.
   J. Donald Hill, M.D., San Francisco, Calif.
   E. Lawson McDonald, M.D., F.A.C.C., London, England

4. **The Sensitivity and Specificity of Exercise Electrocardiography**

   Chairman—Herman K. Hellerstein, M.D., F.A.C.C., Cleveland, Ohio

   Samuel M. Fox, III, M.D., F.A.C.C., Washington, D.C.
   Paul L. McHenry, M.D., Indianapolis, Ind.
   Albert S. Most, M.D., Providence, R.I.

5. **Bedside Techniques in the Evaluation of Coronary Artery Disease**

   Chairman—J. Willis Hurst, M.D., F.A.C.C., Atlanta, Ga.

   Robert L. Krause, M.D., F.A.C.C., Philadelphia, Pa.
   Gordon A. Ewy, M.D., F.A.C.C., Tuscon, Ariz.
   George C. Griffith, M.D., F.A.C.C., La Canada, Calif.
   Oglesby Paul, M.D., F.A.C.C., Chicago, Ill.

6. **Anticoagulant and Antiplatelet Therapy—Indications in Venous and Arterial Disease**

   Chairman—Arthur Selzer, M.D., F.A.C.C., San Francisco, Calif.

   Clark H. Millikan, M.D., F.A.C.C., Rochester, Minn.
   Walter Somerville, M.D., London, England
   Nanette K. Wenger, M.D., F.A.C.C., Atlanta, Ga.

7. **Pacemakers: Theoretical and Practical Considerations in Relation to Prognosis**

   Chairman—Howard B. Burchell, M.D., F.A.C.C., Minneapolis, Minn.

   Michael Bilitch, M.D., Los Angeles, Calif.
   Doris J. W. Escher, M.D., F.A.C.C., Scarsdale, N.Y.
   Rashid A. Massumi, M.D., F.A.C.C., Davis, Calif.

8. **The Controversy over Beta Adrenergic Receptor Blockade**

   Chairman—Henry I. Russek, M.D., F.A.C.C., Staten Island, N.Y.

   Wilbert S. Aronow, M.D., F.A.C.C., Long Beach, Calif.
   Stephen E. Epstein, M.D., Bethesda, Md.
   Donald C. Harrison, M.D., F.A.C.C., Stanford, Calif.
   Steven Wolfson, M.D., New Haven, Conn.

9. **Sudden Death—Identification of and Approach to the Vulnerable Patient**

   Chairman—Bernard Lown, M.D., F.A.C.C., Boston, Mass.

   Nemat O. Borhani, M.D., F.A.C.C., Davis, Calif.
   Charles W. Frank, M.D., Bronx, N.Y.
   William B. Kannel, M.D., F.A.C.C., Framingham, Mass.

1:30 VISIT EXHIBITS

PAUL WOOD REMEMBERED

(Continued)

International Ballroom North, Conrad Hilton Hotel

FRIDAY (continued)

Chairmen: E. Grey Dimond, M.D., F.A.C.C., Kansas City, Mo. Oscar Magidson, M.D., F.A.C.C., Los Angeles, Calif.

P.M.

2:00 **Today's Appreciation of the Eisenmenger-Wood Reaction**—Jane Somerville, M.D., London, England

2:35 **Congestive Heart Failure in Atrial Septal Defect**—Malcolm B. McIlroy, M.D., San Francisco, Calif.

3:05 **Late Complications After Correction of Fallot's Tetralogy**—Samuel Kaplan, M.D., F.A.C.C., Cincinnati, Ohio

3:35 INTERMISSION AND VISIT EXHIBITS

3:50 **Coronary Artery Disease—Antidote to a Stereotype**—Joseph K. Perloff, M.D., F.A.C.C., Washington, D. C.

4:20 **Mechanisms of Dyspnea in Heart Disease**—D. Hywel Davies, M.D., F.A.C.C., Denver, Colo.

4:45 CLOSING REMARKS

CORE CURRICULUM IN CLINICAL CARDIOLOGY

Grand Ballroom, Conrad Hilton Hotel

Chairman: Suzanne B. Knoebel, M.D., F.A.C.C., Indianapolis, Ind.

BEDSIDE OBSERVATION AND LABORATORY AIDS IN THE DIAGNOSIS AND FUNCTIONAL EVALUATION OF:

P.M.

2:00 **Congenital Heart Disease in the Adult**—Noble O. Fowler, M.D., F.A.C.C., Cincinnati, Ohio

2:45 **Valvular Heart Disease**—Moderator—J. Willis Hurst, M.D., F.A.C.C., Atlanta, Ga.

The Aortic Valve—Robert C. Schlant, M.D., F.A.C.C., Atlanta, Ga.

The Mitral Valve—Mark E. Silverman, M.D., F.A.C.C., Atlanta, Ga.

The Utilization of Drugs and Exercise as an Aid in Elucidating Auscultatory Findings—Wayne Siegel, M.D., Atlanta, Ga.

3:30 INTERMISSION AND VISIT EXHIBITS

4:00 **Primary Myocardial Disease**—W. Proctor Harvey, M.D., F.A.C.C., Washington, D. C.

4:45 **Coronary Artery Disease**—Charles K. Friedberg, M.D., F.A.C.C., New York, N.Y.

CARDIOVASCULAR PHARMACOLOGY

International Ballroom South, Conrad Hilton Hotel

Chairman: Harry F. Zinsser, M.D., F.A.C.C., Philadelphia, Pa.

P.M.

2:00 **Reduced Subendocardial Blood Flow and Ventricular Contractile Force Caused by Nitroglycerin**—R. Forman, M.D., E. S. Kirk, Ph.D., J. M. Downey, Ph.D., and Edmund H. Sonnenblick, M.D., F.A.C.C., Boston, Mass.

2:15 **Failure of Intracoronary Nitroglycerine to Alleviate Pacing-Induced Angina**—William Ganz, M.D., F.A.C.C., and Harold S. Marcus, M.D., Los Angeles, Calif.

2:30 **The Beneficial Effects of Nitroglycerin on the Degree of Myocardial Ischemia Occurring During Coronary Occlusion in the Conscious Dog**—David R. Redwood, M.B., Eldon R. Smith, M.D., William E. McCarron, M.D., and Stephen E. Epstein, M.D., Bethesda, Md.

2:45 **Improved Left Ventricular Function During Nitroprusside Infusion in Acute Myocardial Infarction**—Joseph A. Franciosa, M.D., Nabil H. Guiha, M.D., Ernesto Rodriguera, M.D., Constantinos Limas, M.D., and Jay N. Cohn, M.D., F.A.C.C., Washington, D.C.

3:00 **Effects of Propranolol and L-Norephinephrine in Acute Myocardial Infarction in Man**—Hiltrud Mueller, M.D., F.A.C.C., Stephen M. Ayres, M.D., F.A.C.C., and William J. Grace, M.D., F.A.C.C., New York, N.Y.

3:15 **Enhancement of Myocardial Function During Hypoxia by Increased Glucose Availability**—Ezra A. Amsterdam, M.D., F.A.C.C., D. Foley, Rashid A. Massumi, M.D., F.A.C.C., Robert F. Zelis, M.D., F.A.C.C., and Dean T. Mason, M.D., F.A.C.C., Davis Calif.

3:30 INTERMISSION AND VISIT EXHIBITS

Chairman: George C. Griffith, M.D., F.A.C.C., La Canada, Calif.

4:00 **Myocardial Glycogen Content and Myocardial Function During Anoxia**—Robert L. Hewitt, M.D., and David M. Lolley, M.D., New Orleans, La.

4:15 **Reduction in Experimental Myocardial Infarct Size by Glucose-Insulin-Potassium Administration**—Peter R. Maroko, M.D., P. Libby, Burton E. Sobel, M.D., F.A.C.C., Colin M. Bloor, M.D., F.A.C.C., Harley D. Sybers, M.D., William E. Shell, M.D., and Eugene Braunwald, M.D., F.A.C.C., La Jolla, Calif.

4:30 **Dopamine in the Treatment of Refractory Cardiogenic Shock**—Donald C. Harrison, M.D., F.A.C.C., Stanford, Calif.

4:45 **Comparison of the Beta Adrenergic Blocking Properties and Negative Inotropic Effects of Oxprenolol and Propranolol in Patients**—Yves Choquet, M.D., Robert J. Capone, M.D., Dean T. Mason, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., and Robert F. Zelis, M.D., F.A.C.C., Davis, Calif.

5:00 **The Unpredictability of the Response of Idiopathic Hypertrophic Subaortic Stenosis Patients to Oral Propranolol**—William John Powell, Jr., M.D., Richard B. Whiting, M.D., Robert E. Dinsmore, M.D., Charles A. Sanders, M.D., Boston, Mass.

5:15 **Cardiac Effects of a Cocktail**—Lawrence A. Gould, M.D., F.A.C.C., Mohammad Zahir, M.D., F.A.C.C., Robert F. Gomprecht, M.D., F.A.C.C., and Anthony DeMartino, M.D., Bronx, N.Y.

CARDIOGENIC SHOCK

Continental Room, Conrad Hilton Hotel

Chairman: Max Harry Weil, M.D., F.A.C.C., Los Angeles, Calif.

P.M.

2:00 **Identification of Clinical Subsets in Cardiogenic Shock**—T. A. Don Michael M.D., F.A.C.C., James S. Forrester, M.D., H. N. Allen, M.D., and H. J. C. Swan, M.D., Ph.D., F.A.C.C., Los Angeles, Calif.

FRIDAY (continued)

2:15 **Objective Index of Hemodynamic Status for Quantitation of Severity and Prognosis of Shock Complicating Myocardial Infarction**—Protasio Da Luz, M.D., Abdelmonem A. Afifi, Ph.D., Vinnie Liu, M.S., S. Herbert Shubin, M.D., F.A.C.C., and Max Harry Weil, M.D., Ph.D., F.A.C.C., Los Angeles, Calif.

2:30 **Electrocardiographic Localization of Injury in Acute Myocardial Infarction: Relation to Left Ventricular Function and Cardiac Pump Failure**—J. L. Hughes, M.D., Richard R. Miller, M.D., Anthone Salel, M.D., Rashid A. Massumi, M.D., F.A.C.C., Robert F. Zelis, M.D., F.A.C.C., Dean T. Mason, M.D., F.A.C.C., and Ezra A. Amsterdam, M.D., F.A.C.C., Davis, Calif.

2:45 **A Method of Quantifying the Need for Surgical Therapy in Clinical Myocardial Infarction Shock**—John H. Siegel, M.D., Edward J. Farrell, B.S., Isaac Lewin, M.D., and David Bregman, M.D., New York, N.Y.

3:00 **Plasma Volume in Shock Associated with Myocardial Infarction**—Protasio Da Luz, M.D., S. Herbert Shubin, M.D., F.A.C.C., Max Harry Weil, M.D., Ph.D., F.A.C.C., and Leon Stein, M.D., Los Angeles, Calif.

3:15 **Production of a Myocardial Depressant Factor in Shock Following Acute Myocardial Infarction: Preliminary Evaluation of Treatment with Methylprednisolone**—Richard S. Crampton, M.D., F.A.C.C., S. L. Wangensteen, M.D., W. L. Lovett, M.D., J. N. Morris, Jr., B.A., R. H. Harris, M.D., R. Weitzmann, M.D., T. M. Glenn, Ph.D., and A. M. Lefer, Ph.D., Charlottesville, Va.

3:30 INTERMISSION AND VISIT EXHIBITS

Chairman: Dwight E. Harken, M.D., F.A.C.C., Boston, Mass.

4:00 **Hyperosmolal State Following Cardiac Arrest**—Joao A. Mattar, M.D., Max Harry Weil, M.D., Ph.D., F.A.C.C., S. Herbert Shubin, M.D., F.A.C.C., and Leon Stein, M.D., Los Angeles, Calif.

4:15 **Medical Versus Surgical Management of Cardiogenic Shock**—Syed Z. Abbas, M.D., K. R. Shankar, M.D., G. Cohen, M.D., Y. Akyrekli, M.D., W. J. Keon, M.D., Ottawa, Can.

4:30 **Physiologic Effects of Intra-aortic Balloon Pumping in Cardiogenic Shock**—Stephen Scheidt, M.D., and Cooperating Investigators, Balloon Pump Cooperative Study, Los Angeles, Calif., Detroit, Mich., New York, N.Y., and Seattle, Wash.

4:45 **Hemodynamic Studies with a Permanently Implanted Left Ventricular Assist Device**—Steve Phillips, Dov Jaron, Ph.D., Paul Freed, M.S., George Zorzi, M.D., Alejandro Aris, M.D., and Adrian Kantrowitz, M.D., F.A.C.C., Detroit, Mich.

5:00 **The Beneficial Effects of the Combined Use of Vasoconstrictors and Intra-Aortic Balloon Counterpulsation in the Therapy of Cardiogenic Shock**—Mario Feola, M.D., Raymond R. Limet, M.D., and Gerald Glick, M.D., Chicago, Ill.

5:15 **Twenty-Four Hour Left Ventricular Bypass in the Unanesthetized Dog: A Study Employing Transthoracic Cannulation and a Paracorporeal Roller Pump**—S. Kazama, M.D., E. H. Lerner, D.V.M., H. Metz, B.S., J. A. Waldhausen, M.D., F.A.C.C., and William S. Pierce, M.D., F.A.C.C. Philadelphia, Pa., Hershey, Pa., and Bethesda, Md.

CLINICAL CONVERSATIONS WITH THE MASTER TEACHERS

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Parlors 534, 545, 546, 547, Conrad Hilton Hotel

P.M.

2:00-3:00—Group I

4:00-5:00—Group II

Master Teachers: Leonard S. Dreifus, M.D., F.A.C.C., Narberth, Pa.
James J. Leonard, M.D., F.A.C.C., Pittsburgh, Pa.
Henry D. McIntosh, M.D., F.A.C.C., Houston, Tex.
H. J. C. Swan, M.D., F.A.C.C, Los Angeles, Calif.

CINE SEMINAR

Crystal Room, Sheraton Blackstone Hotel

P.M.

3:00 to 5:30
Film titles to be announced

YOUNG INVESTIGATORS' AWARDS COMPETITION

Waldorf Room, Conrad Hilton Hotel

Chairman: J. A. Abildskov, M.D., F.A.C.C., Salt Lake City, Utah

P.M.

3:30 to 5:00
Finalists' Presentations

SATURDAY, MARCH 4

A.M.

8:00 Registration—Lower Lobby, Conrad Hilton Hotel

CONTROVERSIES IN CARDIOLOGY

International Ballrooms North and South, Conrad Hilton Hotel

Chairmen: Lawrence S. Cohen, M.D., F.A.C.C., New Haven, Conn.
Eliot Corday, M.D., F.A.C.C., Los Angeles, Calif.

A.M.

9:00 **Is Saphenous Vein Bypass Grafting the Treatment of Choice for Impending Myocardial Infarction?**
Proponent: W. Dudley Johnson, M.D., Milwaukee, Wis.
Antagonist: George E. Burch, M.D., F.A.C.C., New Orleans, La.

SATURDAY (continued)

9:35 **Is Catheterization Necessary in Children Before Operation?**
Proponent: William Rashkind, M.D., Philadelphia, Pa.
Antagonist: James Dushane, M.D., Rochester, Minn.

10:10 **How Effective is Aortic Balloon Pumping in Cardiogenic Shock?**
Proponent: Adrian Kantrowitz, M.D., F.A.C.C., Detroit, Mich.
Antagonist: Samuel Meerbaum, Ph.D., Los Angeles, Calif.

10:45 INTERMISSION AND VISIT EXHIBITS

11:15 **Does Maximal Exercise Stress Testing Increase the Sensitivity in the Detection of Latent Ischemic Heart Disease?**
Proponent—Robert A. Bruce, M.D., F.A.C.C., Seattle, Wash.
Antagonist—Naip Tuna, M.D., Ph.D., F.A.C.C., Minneapolis, Minn.

SELF-ASSESSMENT CLASSROOM

Bel Air Room, Conrad Hilton Hotel

A.M.

9:00 to 5:00 p.m.

CORE CURRICULUM IN CLINICAL CARDIOLOGY

Grand Ballroom, Conrad Hilton Hotel

Chairman: Leonard S. Dreifus, M.D., F.A.C.C., Narberth, Pa.

ADVANCES IN THE THERAPY OF:

A.M.

8:30 **Arrhythmias**—Borys Surawicz, M.D., F.A.C.C., Lexington, Ky.

9:00 **Bacterial Endocarditis**—Edward L. Quinn, M.D., Detroit, Mich.

9:30 **Coronary Artery Disease (Surgery)**—William Likoff, M.D., F.A.C.C., Philadelphia, Pa.

10:00 INTERMISSION AND VISIT EXHIBITS

10:30 **Pre-Hospital Phase of Myocardial Infarction**—Paul N. Yu, M.D., F.A.C.C., Rochester, N.Y.

11:00 **Acute Myocardial Infarction**—H. J. C. Swan, M.D., F.A.C.C., Los Angeles, Calif.

11:30 **Valvular Disease**—Henry D. McIntosh, M.D., F.A.C.C., Houston, Tex.

CLINICAL CONVERSATIONS WITH THE MASTER TEACHERS

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Parlors 534, 545, 546, 547, Conrad Hilton Hotel

A.M.

9:00-10:00—Group I

11:00-12:00—Group II

Master Teachers: Charles Fisch, M.D., F.A.C.C., Indianapolis, Ind.
William J. Grace, M.D., F.A.C.C., New York, N.Y.
Charles A. Hufnagel, M.D., F.A.C.C., Washington, D. C.
William C. Roberts, M.D., F.A.C.C., Bethesda, Md.

VALVULAR DISEASE

Continental Room, Conrad Hilton Hotel

Chairman: Henry D. McIntosh, M.D., F.A.C.C., Houston, Tex.

A.M.

8:30 **On the Mechanism of Diastolic Rumbles**—Nicholas J. Fortuin, M.D., Ernest Craige, M.D., F.A.C.C., Chapel Hill, N. C.

8:45 **Postural Changes in Left Ventricular and Mitral Valvular Dynamics in the Systolic Click—Late Systolic Murmur Syndrome**—Mary E. Fontana, M.D., Charles F. Wooley, M.D., Richard F. Leighton, M.D., F.A.C.C., and Richard P. Lewis, M.D., F.A.C.C., Columbus, Ohio

9:00 **Angiographic Analysis of Left Ventricular Performance in Patients with Rheumatic Mitral Stenosis**—John A. Holzer, B.A., Joel S. Karliner, M.D., Robert A. O'Rourke, M.D., Kirk L. Peterson, M.D., and Nina S. Braunwald, M.D., F.A.C.C., La Jolla, Calif.

9:15 **Comparative Mechanisms of Ventricular Dysfunction in Aortic and Mitral Stenosis Associated with Coronary Artery Disease**—Gregory J. Scampardonis, M.D., Antonio G. Hermosillo, M.D., Jaime J. Arriaga, M.D., Demetrios Kimbiris, M.D., and Leonard S. Dreifus, M.D., F.A.C.C., Philadelphia, Pa.

9:30 **Abnormalities of Left Ventricular Contractility in Isolated Right Ventricular Overload**—Antone Salel, M.D., Dean T. Mason, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., and Robert F. Zelis, M.D., F.A.C.C., Davis, Calif.

9:45 **Hemodynamic Changes Accompanying Exertional Syncope in Dogs with Right Ventricular Outflow Obstruction**—Robert E. Goldstein, M.D., Allen A. Nimetz, M.D., Joseph E. Pierce, D.V.M., and Stephen E. Epstein, M.D., Bethesda, Md.

10:00 INTERMISSION AND VISIT EXHIBITS

Chairman: John Ross, Jr., M.D., F.A.C.C., San Diego, Calif.

10:30 **Healed Valvular Infective Endocarditis**—Neil A. Buchbinder, M.D., Andrew G. Morrow, M.D., F.A.C.C., and William C. Roberts, M.D., F.A.C.C., Bethesda, Md.

10:45 **Papillary Muscle Necrosis in Active Valvular Infective Endocarditis**—William C. Roberts, M.D., F.A.C.C., and Neil A. Buchbinder, M.D., Bethesda, Md.

11:00 **Ten Year Experience with Isolated Starr-Edwards Mitral Valve Replacement**—Herbert A. Oxman, M.D., Daniel C. Connolly, M.D., F.A.C.C., Dwight C. McGoon, M.D., Robert B. Wallace, M.D., Gordon K. Danielson, M.D., F.A.C.C., and James R. Pluth, M.D., Rochester, Minn.

SATURDAY (continued)

11:15 **Anatomic Studies on Cloth-Covered Starr-Edwards Prosthetic Valves Implanted for Longer than Two Months**—William C. Roberts, M.D., F.A.C.C., Robert L. Reis, M.D., Victor J. Ferrans, M.D., and Andrew G. Morrow, M.D., F.A.C.C., Bethesda, Md.

11:30 **An Improved Mitral Valve Prosthesis**—Arthur C. Beall, Jr., M.D., F.A.C.C., George C. Morris, Jr., M.D., F.A.C.C., George P. Noon, M.D., F.A.C.C., George J. Reul, Jr., M.D., and Gene A. Guinn, M.D., Houston, Tex.

11:45 **Structural Alterations in Tissue Cardiac Valves Implanted in Humans and Cows**—John W. Yarbrough, M.D., William C. Roberts, M.D., F.A.C.C., Jefferson F. Hollingsworth, M.D., David Melvin, M.D., David M. Conkle, M.D., and Robert L. Reis, M.D., Bethesda, Md.

LUNCHEON PANELS

Conrad Hilton and Sheraton Blackstone Hotels

P.M.

12:00 to 1:30

1. **Management of Congenital Aortic Stenosis**

   Chairman—Julien I. E. Hoffman, M.D., San Francisco, Calif.

   William Bernhardt, M.D., Boston, Mass.
   William F. Friedman, M.D., F.A.C.C., San Diego, Calif.
   William C. Roberts, M.D., F.A.C.C., Bethesda, Md.

2. **The Terminal Cardiac Patient—Transplant, Artificial Heart Or . . . ?**

   Chairman—Charles K. Friedberg, M.D., F.A.C.C., New York, N.Y.

   Denton A. Cooley, M.D., F.A.C.C., Houston, Tex.
   John F. Goodwin, M.D., F.A.C.C., London, England
   Charles A. Hufnagel, M.D., F.A.C.C., Washington, D.C.
   Adrian Kantrowitz, M.D., F.A.C.C., Detroit, Mich.

3. **Recognition and Management of Pulmonary Embolic Disease**

   Chairman—Myron Stein, M.D., Pawtucket, R.I.

   Paul A. Ebert, M.D., F.A.C.C., New York, N.Y.
   J. Hirsh, M.D., Hamilton, Ont., Can.
   Paul M. Stevens, M.D., Houston, Tex.

4. **The Clinical Quantification of Myocardial Infarction**

   Chairman—Louis Cohen, M.D., F.A.C.C., Chicago, Ill.

   Heinz Bauer, M.D., Washington, D.C.
   Eugene L. Coodley, M.D., F.A.C.C., Philadelphia, Pa.
   S. Herbert Shubin, M.D., F.A.C.C., Los Angeles, Calif.
   Burton E. Sobel, M.D., F.A.C.C., San Diego, Calif.

5. **The Intermediate Coronary Care Unit**

   Chairman—William J. Grace, M.D., F.A.C.C., New York, N.Y.

   James E. Crockett, M.D., F.A.C.C., Kansas City, Mo.
   Alfred Soffer, M.D., F.A.C.C., Chicago, Ill.
   Sylvan L. Weinberg, M.D., F.A.C.C., Dayton, Ohio

6. **Indications for and Hazards of Coronary Arteriography**

   Chairman—Robert C. Schlant, M.D., F.A.C.C., Atlanta, Ga.

   Henry LeRoy Abrams, M.D., Boston, Mass.
   Goffredo G. Gensini, M.D., F.A.C.C., Syracuse, N.Y.
   Charles B. Mullins, M.D., Dallas, Tex.

7. **New Diuretics—Boon or Bane?**

   Chairman—Albert N. Brest, M.D., F.A.C.C., Philadelphia, Pa.

   Frank A. Finnerty, Jr., M.D., F.A.C.C., Washington, D.C.
   Melvin M. Scheinnan, M.D., F.A.C.C., Burlington, Calif.
   Robert H. Seller, M.D., F.A.C.C., Rydal, Pa.

8. **The Primary Prophylaxis of Coronary Artery Disease**

   Chairman—Robert F. Zelis, M.D., F.A.C.C., Davis, Calif.

   Aram V. Chobanian, M.D., Boston, Mass.
   William B. Kannel, M.D., F.A.C.C., Framingham, Mass.
   Jeremiah Stamler, M.D., F.A.C.C., Chicago, Ill.

9. **Current Status of Fascicular Block**

   Chairman—Charles Fisch, M.D., F.A.C.C., Indianapolis, Ind.

   Cesar Castillo, M.D., Miami, Fla.
   George K. Massing, M.D., Birmingham, Ala.
   Kenneth M. Rosen, M.D., F.A.C.C., Chicago, Ill.

1:30 VISIT EXHIBITS

BUSINESS MEETING OF THE COLLEGE

International Ballroom North, Conrad Hilton Hotel

Chairman: Forrest H. Adams, M.D., F.A.C.C., President of the College, Los Angeles, Calif.

P.M.

1:45 to 2:00

The Annual Business Meeting for the transaction of necessary College business will begin promptly at 1:45 p.m. All Fellows of the College have an obligation to attend, to hear the report of the President and Secretary of the College, and to take part in the election of officers and trustees.

International Ballroom North, Conrad Hilton Hotel

Chairman: William A. Sodeman, M.D., F.A.C.C., Philadelphia, Pa.

P.M.

2:00 THIRD ANNUAL LOUIS F. BISHOP LECTURESHIP

Cardiomyopathies: Spectrum and Current Understanding—John F. Goodwin, M.D., F.A.C.C., London, England

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PROGRESS REPORTS—1972

International Ballroom North, Conrad Hilton Hotel

Chairman: Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

Co-Chairman: Harold T. Dodge, M.D., F.A.C.C., Seattle, Wash.

P.M.

2:30 **Problem-Oriented Medical Records: Concepts and Advances**—J. Willis Hurst, M.D., F.A.C.C., Atlanta, Ga.

2:50 **Trends and Developments in NHLI Research and Training Programs**—Theodore Cooper, M.D., F.A.C.C., Bethesda, Md.

3:10 **Advances in the Prevention of Coronary Artery Disease**—William B. Kannel, M.D., F.A.C.C., Framingham, Mass.

3:30 INTERMISSION AND VISIT EXHIBITS

4:00 **Regulation of the Pulmonary Circulation**—Alfred P. Fishman, M.D., F.A.C.C., Philadelphia, Pa.

SATURDAY (continued)

4:20 **Peripheral Circulatory Compensatory Mechanisms in Congestive Heart Failure**—Robert F. Zelis, M.D., F.A.C.C., Davis, Calif.

4:40 **Symptomatic Heart Disease in the Newborn**—Julian I. E. Hoffman, M.D., San Francisco, Calif.

5:00 Adjourn

ACUTE MYOCARDIAL INFARCTION

Continental Room, Conrad Hilton Hotel

Chairman: H. J. C. Swan, M.D., F.A.C.C., Los Angeles, Calif.

P.M.

2:00 **Noninvasive Determination of Infarct Size Five Hours after Coronary Occlusion in the Conscious Dog**—William E. Shell, M.D., Burton E. Sobel, M.D., F.A.C.C., James W. Covell, M.D., and John F. Lavelle, M.S., La Jolla, Calif.

2:15 **Myocardial Infarct Size in Man Assessed by Serial Serum Creatine Phosphokinase Changes**—Gerald F. Breshnahan, M.D., William E. Shell, M.D., Burton E. Sobel, M.D., F.A.C.C., and Richard D. Yoder, M.D., La Jolla, Calif.

2:30 **Is Coronary Sinus Monitoring in Acute Myocardial Infarction Useful? (Studies in 25 Patients)**—Hiltrud Mueller, M.D., F.A.C.C., Stephen M. Ayres, M.D., F.A.C.C., James T. Mazzara, M.D., and William J. Grace, M.D., F.A.C.C., New York, N.Y.

2:45 **Acute Myocardial Infarction: Myocardial Perfusion and Metabolism**—James Forrester, M.D., George Diamond, M.D., William Ganz, M.D., F.A.C.C., and H. J. C. Swan, M.D., Ph.D., F.A.C.C., Los Angeles, Calif.

3:00 **Electrical Impedance Cardiogram: Measurements from Hearts with Acute Injury**—Bernard G. Krohn, M.D., F.A.C.C., David A. Swan, M.D., F.A.C.C., Jerome H. Kay, M.D., F.A.C.C., and Oscar Magidson, M.D., F.A.C.C., Los Angeles, Calif.

3:15 **Left Ventricular Function and Coronary Anatomy Before and After Myocardial Infarction**—Douglas K. Stewart, M.D., Glen W. Hamilton, M.D., John A. Murray, M.D., F.A.C.C., and J. W. Kennedy, M.D., Seattle, Wash.

3:30 INTERMISSION AND VISIT EXHIBITS

Chairman: William J. Grace, M.D., F.A.C.C., New York, N.Y.

4:00 **Regional Left Ventricular Performance in the Year Following Myocardial Infarction**—Bolling J. Feild, M.D., Richard O. Russell, Jr., M.D., F.A.C.C., and Charles E. Rackley, M.D., F.A.C.C., Birmingham, Ala.

4:15 **Hemodynamic Changes One Year After Acute Myocardial Infarction**—Robert M. Davidson, M.D., Galen S. Wagner, M.D., Thomas L. Haney, Barry W. Ramo, M.D., Robert E. Whalen, M.D., F.A.C.C., and Andrew G. Wallace, M.D., Durham, N.C.

4:30 **Heart Size and Left Ventricular Function in the Year Following Myocardial Infarction**—Richard O. Russell, Jr., M.D., F.A.C.C., Bolling J. Feild, M.D., and Charles E. Rackley, M.D., F.A.C.C., Birmingham, Ala.

4:45 **Results of Early Surgical Repair of Ventricular Septal Defects Following Myocardial Infarction**—Anthony F. Graham, M.D., Norman E. Shumway, M.D., F.A.C.C., and Donald C. Harrison, M.D., F.A.C.C., Stanford, Calif.

CINE SEMINAR

Crystal Ballroom, Sheraton Blackstone Hotel

P.M.

3:00 to 5:00
Film titles to be announced

ELECTROPHYSIOLOGY

International Ballroom South, Conrad Hilton Hotel

Chairman: Borys Surawicz, M.D., F.A.C.C., Lexington, Ky.

P.M.

2:00 **Refractoriness of the Accessory Pathway and Mechanisms of Reentry in the W-P-W Phenomenon**—Sun H. Lau, M.D., Mark E. Josephson, M.D., John J. Gallagher, M.D., Anthony R. Caracta, P. Jacob Varghese, M.D., and Anthony N. Damato, M.D., Staten Island, N.Y.

2:15 **A Study of the Ventricular Activation Process in Preexcitation Syndrome using His Bundle and 1 mm Apart Bipolar Electrograms**—Cesar A. Castillo, M.D., Agustin Castellanos, Jr., M.D., F.A.C.C., Robert J. Myerburg, M.D., and Abdul S. Agha, M.D., Miami, Fla.

2:30 **Second Degree Wenckebach Type A-V Block Due to Block Within the Atrium**—Onkar S. Narula, M.D., Manfred Runge, M.D., and Philip Samet, M.D., F.A.C.C., Miami Beach, Fla.

2:45 **Pseudo Type II A-V Block**—P. Jacob Varghese, M.D., Anthony N. Damato, M.D., Robert N. Schnitzler, M.D., John J. Gallagher, M.D., and Sun H. Lau, M.D., Staten Island, N.Y.

3:00 **Summation and Voltage Dependency in Rabbit A-V Nodal Fibers**—Douglas P. Zipes, M.D., Carlos Mendez, M.D., and Gordon K. Moe, M.D., Ph.D., Indianapolis, Ind., and Utica, N.Y.

3:15 **Dependence of A-V Junctional Automaticity on Sympathetic Tone**—Kay Millar, M.D., F. Urthaler, M.D., Mary J. Burgess, M.D., J. A. Abildskov, M.D., F.A.C.C., and Thomas N. James, M.D., F.A.C.C., Birmingham, Ala.

3:30 INTERMISSION AND VISIT EXHIBITS

Chairman: Alberto Benchimol, M.D., F.A.C.C., Phoenix, Ariz.

4:00 **Manifest and Concealed Reentry: A Mechanism of A-V Nodal Wenckebach in Man**—John J. Gallagher, M.D., Anthony N. Damato, M.D., P. Jacob Varghese, M.D., and Sun H. Lau, M.D., Staten Island, N.Y.

4:15 **Ectopic Rhythms Arising From Anterior and Posterior Fascicles of the Left Bundle Branch in Anterior and Posterior Myocardial Infarctions**—Rashmid A. Massumi, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., Antone F. Salel, M.D., Richard R. Miller, M.D., Zaka-Ud D. Vera, M.D., Gungor E. Ertem, M.D., F.A.C.C., and Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

4:30 **H-V Prolongation in Left Bundle Branch Block: Clinical and Electrocardiographic Correlations**—Ali A. Ehsani, M.D., Kenneth M. Rosen, M.D., F.A.C.C., Mohammed Jamil, M.D., Rolf M. Gunnar, M.D., F.A.C.C., and Shahbudin H. Rahimtoola, M.D., F.A.C.C., Chicago, Ill.

SATURDAY (continued)

4:45 **Ionic Basis of Low Resting Potential in Diseased Human Heart**—Robert E. Ten Eick, Ph.D., Ramalingaer Parameswaran, M.D., Lloyd E. Solberg, M.D., and Donald H. Singer, M.D., F.A.C.C., Chicago, Ill.

TWENTY-FIRST ANNUAL CONVOCATION

Grand Ballroom, Conrad Hilton Hotel

P.M.

6:30 Processional

Invocation

Introduction of Distinguished Guests and Officers

Conferring of Fellowships by the President

Presentation of Special Awards

Presentation of the Convocation Medal to the Convocation Lecturer

The Convocation Lecture by:
Merlin K. DuVal, M.D., Washington, D. C.
Assistant Secretary for
Health and Scientific Affairs
Department of Health, Education, and Welfare

Installation of New President

Recessional

RECEPTION

International Ballroom South, Conrad Hilton Hotel

P.M.

8:00

DINNER DANCE*

International Ballroom North, Conrad Hilton Hotel

P.M.

9:00

*(Black tie optional)

SUNDAY, MARCH 5

A.M.

8:00 Registration—Lower Lobby—Conrad Hilton Hotel

ECG AND ELECTROPHYSIOLOGY

Grand Ballroom, Conrad Hilton Hotel

Chairman: Charles Fisch, M.D., F.A.C.C., Indianapolis, Ind.

Co-Chairman: Borys Surawicz, M.D., F.A.C.C., Lexington, Ky.

A.M.

9:00 REENTRY AND RECIPROCAL RHYTHMS:
Electrophysiology—Jaok Han, M.D., Ph.D., F.A.C.C., Albany, N.Y.
Electrocardiography—Douglas P. Zipes, M.D., Indianapolis, Ind.

9:30 VULNERABILITY AND FIBRILLATION:
Electrophysiology—Borys Surawicz, M.D., F.A.C.C., Lexington, Ky.
Electrocardiography—Roderick W. Childers, M.D., Chicago, Ill.

10:00 INTERMISSION

10:30 ABERRANCY:
Electrophysiology—Kalman Greenspan, Ph.D., F.A.C.C., Indianapolis, Ind.
Electrocardiography—Rashid A. Massumi, M.D., F.A.C.C., Davis, Calif.

11:00 CONCEALED CONDUCTION:
Electrophysiology—E. Neil Moore, D.V.M., Ph.D., F.A.C.C., Rose Valley, Pa.
Electrocardiography—Richard Langendorf, M.D., F.A.C.C., Chicago, Ill.

11:30 WENCKEBACH STRUCTURE AND EXIT BLOCK
Electrophysiology—Leonard S. Dreifus, M.D., F.A.C.C., Philadelphia, Pa.
Electrocardiography—Alfred Pick, M.D., F.A.C.C., Chicago, Ill.

12:00 AUTOMATICITY:
Electrophysiology—J. Thomas Bigger, Jr., M.D., F.A.C.C., New York, N.Y.
Electrocardiography—Irwin Hoffman, M.D., F.A.C.C., Los Angeles, Calif.

SELF-ASSESSMENT CLASSROOM

Bel Air Room, Conrad Hilton Hotel

A.M.

8:30 to 12:00 noon

CORONARY SURGERY

Williford A and B, Conrad Hilton Hotel

Chairman: Jerome H. Kay, M.D., F.A.C.C., Los Angeles, Calif.

A.M.

8:30 **Survival Experience in Saphenous Vein Bypass Graft Surgery**—Donald R. McRaven, M.D., John A. Walker, M.D., H. David Friedberg, M.D., F.A.C.C., and W. Dudley Johnson, M.D., Milwaukee, Wisc.

8:45 **Objective Evaluation of the Effects of Direct Myocardial Revascularization on Ventricular Performance Utilizing Submaximal Ergometer Exercise Testing**—John C. Manley, M.D., F.A.C.C., W. Dudley Johnson, M.D., Robert J. Flemma, M.D., and Derward Lepley, M.D., F.A.C.C., Milwaukee, Wisc.

9:00 **Results of Aorta-Coronary Bypass Graft Surgery. Comparison with Arterial Implants and Medical Treatment—**

SUNDAY (continued)

G. K. Sehapayak, M.D., Walter M. Allison, M.D., F.A.C.C., Donald G. Pansegrau, M.D., John C. Grammer, M.D., F.A.C.C., William L. Kraus, M.D., F.A.C.C., Dallas, Tex.

9:15 **Indirect Assessment of Coronary Artery Bypass Grafts**—James T. Willerson, M.D., Eldred D. Mundth, M.D., Robert E. Dinsmore, M.D., Harriet Walker, Mortimer J. Buckley, M.D., W. Gerald Austen, M.D., F.A.C.C., Gordon S. Myers, M.D., F.A.C.C., and Charles A. Sanders, M.D., Boston, Mass.

9:30 **Left Ventricular Function Following Successful Aorto-Coronary Vein Bypass**—Glen W. Hamilton, M.D., Douglas K. Stewart, M.D., Kenneth L. Gould, M.D., and J. W. Kennedy, M.D., Seattle, Wash.

9:45 **Influence of Aorto-Coronary Artery Bypass on Left Ventricular Asynergy**—Kanu Chatterjee, M.D., William W. Parmley, M.D., F.A.C.C., H. Sustaita, M.D., Jack M. Matloff, M.D., F.A.C.C., and H. J. C. Swan, M.D., Ph.D., F.A.C.C., Los Angeles, Calif.

10:00 **Progression of Proximal Coronary Arterial Lesions to Total Occlusion after Vein Graft Surgery and its Effects**—George Bousvaros, M.D., F.A.C.C., Muhammad A. Chaudhry, M.D., and Abdul R. Piracha, M.D., Albany, N.Y., and Charleston, W.Va.

10:15 INTERMISSION

Chairman: Charles A. Hufnagel, M.D., F.A.C.C., Washington, D.C.

10:30 **Surgical Management of Acute Evolving Myocardial Infarction: A Coronary Circulatory, Metabolic, and Angiographic Profile**—Leslie Wiener, M.D., F.A.C.C., Hratch Kasparian, M.D., Albert Brest, M.D., F.A.C.C., and John Templeton, M.D., Philadelphia, Pa.

10:45 **Saphenous Vein Bypass Surgery for Impending Myocardial Infarction**—Bernard L. Segal, M.D., F.A.C.C., William Likoff, M.D., F.A.C.C., Hans Van den Broek, M.D., Alberto Adam, M.D., Gumersindo Blanco, M.D., Demetrios Kimbiris, M.D., and Moosa Najmi, M.D., Philadelphia, Pa.

11:00 **Emergency Myocardial Revascularization with Saphenous Vein Bypass Graft**—J. G. Dumesnil, M.D., Gerald T. Gau, M.D., John A. Callahan, M.D., F.A.C.C., James R. Pluth, M.D., Gordon K. Danielson, Jr., M.D., F.A.C.C., and Robert B. Wallace, M.D., Rochester, Minn.

11:15 **Assessment of Aortocoronary Saphenous Vein Bypass Function Utilizing Selective Indicator Dilution Curves**—Alberto Benchimol, M.D., F.A.C.C., Kenneth B. Desser, M.D., F.A.C.C., and James Schumacher, M.D., Phoenix, Ariz.

11:30 **The Cardiac Hemodynamic and Metabolic Responses to Coronary Arterio-Venous Bypass Surgery**—N. Beer, M.D., N. Keller, Ph.D., S. Kline, M.D., E. Tarjan, Ph.D., Robert G. Carlson, M.D., F.A.C.C., and Norman Brachfeld, M.D., F.A.C.C., New York, N.Y.

11:45 **Factors Influencing Flow Through Aorta-Coronary Artery Saphenous Vein Bypass Grafts**—Harold C. Usrchel, Jr., M.D., F.A.C.C., Rolando M. Solis, M.D., Ervin R. Miller, M.D., Maruf A. Razzuk, M.D., and Richard E. Wood, M.D., Dallas, Tex.

CARDIAC FUNCTION

Waldorf Room, Conrad Hilton Hotel

Chairman: Eugene Braunwald, M.D., F.A.C.C., San Diego, Calif.

A.M.

8:30 **The Value of Continuous Monitoring of Cardiac Muscle Performance**—Hooshang Bolooki, M.D., F.A.C.C., Ali Ghahramani, M.D., Leonard Sommer, M.D., F.A.C.C., Louis Lemberg, M.D., F.A.C.C., and Kathleen Boccabella, R.N., Miami, Fla.

8:45 **Rapid On-Line Computer Determination of Left Ventricular Contractility During Pacemaker Tachycardia in Man**—Allen F. Bowyer, M.D., Ronald L. Allen, Roy V. Jutzy, M.D., F.A.C.C., and Varner J. Johns, Jr., M.D., F.A.C.C., Loma Linda, Calif.

9:00 **The Relative Selection Sensitivities of Techniques to Evaluate Myocardial Function in Patients with Left Ventricular Hypertrophy**—Antone Salel, M.D., Dean T. Mason, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., and Robert F. Zelis, M.D., F.A.C.C., Davis, Calif.

9:15 **"Pacing" Left Ventricular Function Curves in Conscious Dogs**—Frances Kraft-Hunter, B.S., M.S., Edward Wm. Hawthorne, M.D., Ph.D., F.A.C.C., Washington, D. C.

9:30 **Role of Adrenergic Inotropic Stimuli in the Systolic Temporal Responses to Exercise**—F. Lopez-Arostegui, M.D., Willard S. Harris, M.D., Jean Maurice Pouget, M.D., F.A.C.C., and Udayan Bhaduri, M.D., Chicago, Ill.

9:45 **Alterations in the Left Ventricular Contractile State During Isometric Exercise in Patients with Coronary Artery Disease**—William H. Gaasch, M.D., Miguel A. Quinones, M.D., Efrain Waisser, M.D., Hans G. Thiel, M.D., James K. Alexander, M.D., F.A.C.C., Houston, Tex.

10:00 **Maximum Rate of Pressure Decline in the Normal, Hypertrophied and Dilated Left Ventricle in Man**—Attilio Reale, M.D., F.A.C.C., Pier A. Gioffre, M.D., Antonio Nigri, M.D., Mario Motolese, M.D., Rome, Italy

10:15 INTERMISSION

Chairman: Charles E. Rackley, M.D., F.A.C.C., Birmingham, Ala.

10:30 **Augmentation of Contractility Following Ischemia in the Isolated Supported Heart**—Robert E. Goldstein, M.D., Jeffrey S. Borer, M.D., and Stephen E. Epstein, M.D., Bethesda, Md.

10:45 **Experimental Left Ventricular Akinesis**—Sidney C. Smith, Jr., M.D., Will Lloyd-Jones, M.D., Juan Serur, M.D., Charles W. Urschel, M.D., Edmund H. Sonnenblick, M.D., F.A.C.C., and F. Henry Ellis, Jr., M.D., Boston, Mass.

11:00 **Experimental Atrial Fibrillation in Conscious Dogs**—Edward Wm. Hawthorne, M.D., Ph.D., F.A.C.C., Joseph E. Hinds, M.D., Ph.D., Washington, D. C.

11:15 **Effects of Varying End-Diastolic Volume and Inotropic State on Ventricular Performance During Atrial Fibrillation in Man**—Joel S. Karliner, M.D., James H. Gault, M.D., Richard J. Bouchard, M.D., John B. Uther, M.D., Kirk L. Peterson, M.D., and Ralph Shabetai, M.D., F.A.C.C., La Jolla, Calif.

SUNDAY (continued)

11:30 **Beat to Beat Alterations in Contractile State as the Mechanism of Spontaneous Pulsus Alternans in Man**—Robert F. Zelis, M.D., F.A.C.C., Robert J. Capone, M.D., Ezra A. Amsterdam, M.D., F.A.C.C., and Dean T. Mason, M.D., F.A.C.C., Davis, Calif.

11:45 **Potentiation of Contraction by Premature Activation in Patients with Normal and Abnormal Left Ventricular Function**—Ralph Shabetai, M.D., F.A.C.C., John B. Uther, M.D., Kirk L. Peterson, M.D., and John Ross, Jr., M.D., F.A.C.C., San Diego, Calif.

EXERCISE TESTING

Beverly Room, Conrad Hilton Hotel

Chairman: Samuel M. Fox, III, M.D., F.A.C.C., Washington, D.C.

A.M.

8:30 **Correlation of the Computer Quantitated ST Response to Exercise with the Arteriographic Location of Coronary Artery Disease**—Paul L. McHenry, M.D., John F. Phillips, M.D., F.A.C.C., and Jamie J. Jacobs, M.D., Indianapolis, Ind.

8:45 **The Correlation of ST Segment Elevations and Axis Shifts in Graded Treadmill Exercise Tests with Coronary Arteriographic Findings**—Fred Hegge, M.D., Naip Tuna, M.D., Ph.D., F.A.C.C., and Howard Burchell, M.D., Ph.D., F.A.C.C., Minneapolis, Minn.

9:00 **Maximal Treadmill Exercise Electrocardiography: Correlations with Coronary Arteriography and Cardiac Hemodynamics**—Carroll M. Martin, M.D., and David R. McConahay, M.D., San Francisco, Calif.

9:15 **Correlation of Degree of ST Segment Depression During Exercise with Presence and Type of Coronary Artery Collaterals**—Paul L. McHenry, M.D., Suzanne B. Knoebel, M.D., F.A.C.C., and John F. Phillips, M.D., F.A.C.C., Indianapolis, Ind.

9:30 **Exercise Induced Ventricular Irritability: Hemodynamic and Angiographic Correlations**—Barry L. Zaret, M.D., and Charles R. Conti, Jr., M.D., F.A.C.C., Baltimore, Md.

9:45 **Exercise Heart Rate and Blood Pressure in ECG Stress Test Design**—L. Thomas Sheffield, M.D., F.A.C.C., and David Roitman, M.D., Birmingham, Ala.

10:00 **Effects of Conditioning on Plasma Catecholamine Levels During Exercise in Patients with Coronary Artery Disease**—Steven Wolfson, M.D., Antonio E. Acosta, M.D., Leslie I. Rose, M.D., Alfred F. Parisi, M.D., and Karl Engelman, M.D., San Antonio, Tex., and Philadelphia, Pa.

10:15 INTERMISSION

DIAGNOSTIC TECHNIQUES

Beverly Room, Conrad Hilton Hotel

Chairman: Bernard L. Segal, M.D., F.A.C.C., Philadelphia, Pa.

A.M.

10:30 **Echocardiographic Diagnosis of Left Atrial Thrombi**—Masanobu Kamigaki, M.D., Thomas Sweatman, M.D., Judith Basford, B.A., Keith E. Cohn, M.D., F.A.C.C., San Francisco, Calif.

10:45 **Echocardiographic Determination of Mitral Valve Flow**—John C. Fischer, M.D., Sonia Chang, B.A., Lee L. Konecke, M.D., and Harvey Feigenbaum, M.D., F.A.C.C., Indianapolis, Ind.

11:00 **Echocardiographic Features of Torn Chordae Tendinae**—John M. Duchak, Jr., M.D., Sonia Chang, B.A., and Harvey Feigenbaum, M.D., F.A.C.C., Indianapolis, Ind.

11:15 **Ultrasound Determination of Mean Fiber Shortening Rate in Man**—Ronald Cooper, B.S., Joel S. Karliner, M.D., Robert A. O'Rourke, M.D., Kirk L. Peterson, M.D., and George Leopold, M.D., La Jolla, Calif.

11:30 **Changes in Left Ventricular Wall Movement Following Exercise, Atrial Pacing and Acute Myocardial Infarction Measured by Reflected Ultrasound**—Charles S. Smithen, M.D., Christopher Warton, B.M., and Edgar Sowton, M.D., F.A.C.C., London, England

11:45 **Serial Evaluation of Left Ventricular Volumes and Posterior Wall Movement in the Acute Phase of Myocardial Infarction Using Diagnostic Ultrasound**—Robert A. Ratshin, M.D., Charles E. Rackley, M.D., F.A.C.C., and Richard O. Russell, Jr., F.A.C.C., Birmingham, Ala.

MYOCARDIAL DISEASE

PDR #2, Conrad Hilton Hotel

Chairman: William C. Roberts, M.D., F.A.C.C., Bethesda, Md.

A.M.

8:30 **The Clinical Course of Cardiomyopathy Associated with Alcoholism**—John G. Demakis, M.D., Shahbudin H. Rahimtoola, M.D., F.A.C.C., George C. Sutton, M.D., Mohammad Jamil, Aloysius Proskey, M.D., Kenneth M. Rosen, M.D., F.A.C.C., and Rolf M. Gunnar, M.D., F.A.C.C., Chicago, Ill.

8:45 **The Clinical Triad of Traumatic Ventricular Septal Defect, Occlusion of Left Anterior Descending Coronary Artery and Ventricular Aneurysm**—Lawrence S. Cohen, M.D., F.A.C.C., Dean T. Mason, M.D., F.A.C.C., Ezra A. Amsterdam, M.D., F.A.C.C., William C. Roberts, M.D., F.A.C.C., J. Edward Rosenthal, M.D., and Robert F. Zelis, M.D., F.A.C.C., Davis, Calif. and Bethesda, Md.

9:00 **Near Miss "Pseudo-Comlications" of Cardiac Catheterization**—Frank J. Hildner, M.D., Roger P. Javier, M.D., K. Ramaswamy, M.D., F.A.C.C., Philip Samet, M.D., F.A.C.C., Miami Beach, Fla.

9:15 **Electrophysiological Properties of Atrial and Ventricular Muscle from Cats with Experimentally Induced Heart Failure and Hypertrophy**—Henry Gelband, M.D., and Arthur L. Bassett, Ph.D., New York, N.Y.

9:30 **Adenyl Cyclase Activity in Experimental Myocardial Hypertrophy**—Anthony F. Cutilletta, M.D., Otto G. Thilenius, M.D., Ph.D., and René A. Arcilla, M.D., F.A.C.C., Chicago, Ill.

9:45 **Myosins From Right and Left Ventricle: Comparison of ATPase Activities and Substructure**—Jack J. Kleid, M.D., Michihiko Tada, M.D., and Arnold M. Katz, M.D., F.A.C.C., New York, N.Y.

10:00 **The Role of Platelet Aggregation in Catecholamine Induced Cardiac Necrosis: Electron Microscopic and Drug Studies**—Jacob I. Haft, M.D., Kenneth Gershengorn, M.D., Paul Kranz, M.D., Frank Albert, M.D., Rolf Oestreicher, M.D., Kazem Fani, M.D., New York, N.Y.

10:15 INTERMISSION

SUNDAY (continued)

PULMONARY EMBOLISM, COAGULATION DEFECTS, AND HYPERTENSION

PDR #2, Conrad Hilton Hotel

Chairman: Hilliard J. Katz, M.D., F.A.C.C., San Francisco, Calif.

A.M.

10:30 **Massive Acute Pulmonary Embolism-Deceivingly Non-Specific Manifestations**—Nanette K. Wenger, M.D., F.A.C.C., Paul D. Stein, M.D., and Park W. Willis, III, M.D., F.A.C.C., Atlanta, Ga.

10:45 **Intravascular Hemolysis and Thrombocytopenia in Left Ventricular Outflow Obstruction**—Robert Jacobsen, M.D., Joseph K. Perloff, M.D., F.A.C.C., and Charles Rath, M.D., Washington, D.C.

11:00 **Disseminated Intravascular Coagulation Complicating Severe Congestive Heart Failure**—Samuel B. Itscoitz, M.D., and Stephen E. Epstein, M.D., Bethesda, Md.

11:15 **Circulatory Responses to Graded Stimulation of the Carotid Chemoreceptors**—L. C. Pelletier, M.D., and John T. Shepherd, M.D., Rochester, Minn.

11:30 **Role of Blood Pressure in the Development of Congestive Heart Failure: The Framingham Study**—William B. Kannel, M.D., F.A.C.C., William P. Castelli, M.D., Patricia M. McNamara, Patrick A. McKee, M.D., and Manning Feinleib, M.D., Framingham, Mass., Durham, N.C., and Washington, D.C.

11:45 **The Nature of the Intrarenal Stimulus Eliciting Renal Hypertension**—Carlos M. Ferrario, M.D., and James W. McCubbin, M.D., Cleveland, Ohio

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Chairman: Charles G. Roland, MD, Rochester, Minn.

Deadline for registration: February 15, 1972

For further information write Charles G. Roland, MD, Chairman, Department of Biomedical Communications, Mayo Foundation, Rochester, Minn. 55901.

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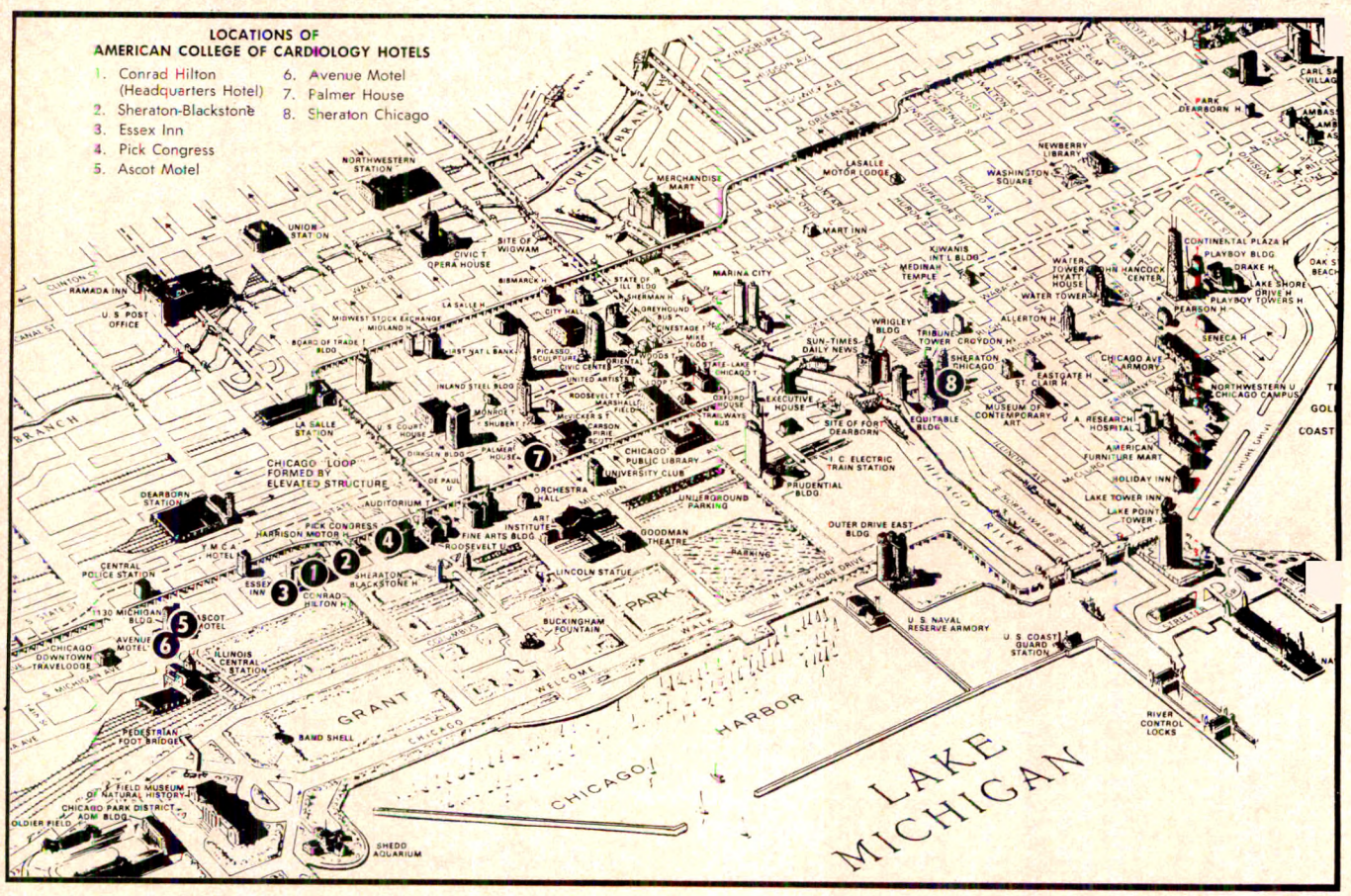
3	Essex Inn	$23.00 - $26.00	$29.00 - $35.00	$29.00 - $35.00	$50.00 - $90.00
4	Pick Congress	$21.00 - $40.00	$31.00 - $50.00	$31.00 - $50.00	$50.00 - $180.00
5	Ascot Motel	$20.00 - $23.00	$27.00 - $32.00	$27.00 - $32.00	$50.00 - $55.00
6	Avenue Motel	$17.00 - $20.00	$23.00 - $26.00	$23.00 - $26.00	—
7	Palmer House	$22.00 - $38.00	$38.00 - $44.00	$38.00 - $46.00	$84.00 and up
8	Sheraton Chicago	$23.00 - $29.00	$31.00 - $37.00	$31.00 - $37.00	$50.00 - $70.00



ACC News: Continuing Medical Education

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

JAN. 6–7 **Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** William W. Parmley, FACC and H.J.C. Swan, co-directors. Cedars Sinai Medical Center, Los Angeles, Calif.

JAN. 9–11 **Myocardial Infarction: New Look at an Old Subject.** John H. K. Vogel, FACC, Bruce C. Paton and Robert Eliot, co-directors. Opticon Theater, Snowmass-at-Aspen, Aspen, Colo.

JAN. 12–14 **Controversies in Cardiovascular Medicine: Practical Aspects** James R. Jude, FACC; George M. Callard, Mary Jane Jesse and Robert Myerburg, co-directors. Sheraton Four Ambassadors Hotel, Miami, Fla.

FEB. 7–9 **The Acute Cardiac Emergency.** Robert S. Eliot, FACC and Gerald Chaplin, co-directors. Ponte Vidra Club, Jacksonville, Fla.

MAR. 20–22 **Electrocardiographic Interpretation of Arrhythmias: A Physiologic Approach.** Charles Fisch, FACC, director, Indiana University Medical Center, Indianapolis, Ind.

MAR. 20–25 **Consultants' Course in Cardiology.** Simon Dack, FACC, Arnold M. Katz, FACC and Robert S. Litwak, FACC, directors. Mount Sinai School of Medicine, New York, N. Y.

APR. 3–12 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 5–7 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 12–13 **The Total Coronary Care System—The Community and The Hospital.** Sylvan L. Weinberg, FACC, C. W. Immt and Joseph M. Wilson, FACC, co-directors. The Sheraton-Dayton Hotel, Dayton, Ohio.

APR. 17–20 **Current Concepts in Cardiology 1972.** Philip R. Akre, FACC and John A. Bower, MD, directors. Riviera Hotel, Las Vegas, Nev.

MAY 8–12 **The Medical and Surgical Treatment of Cardiovascular Disease.** J. Willis Hurst, FACC and W. Dean Warren, MD, directors. Co-sponsored by ACC and Council on Clinical Cardiology of the American Heart Association. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 12–13 **Computer Applications in Electrocardiography.** C. A. Caceres, FACC, director, Sheraton Park Hotel, Washington, D. C.

MAY 18–19 **Heart Sounds and Murmurs: An Audiovisual Presentation.** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, Ind.

MAY 25–27 **A Critical Approach to Cardiovascular Diagnosis.** Arthur Selzer, FACC, director. Jack Tar Hotel, San Francisco, Calif.

SEPT. 8–10 **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, director. Queen Elizabeth Hotel, Montreal, Quebec, Canada.

SEPT. 13–15 **The Clinical Manifestations of Congenital Heart Disease from Birth through Adulthood.** Joseph K. Perloff, FACC and Antonio C. DeLeon, Jr, FACC, directors. Georgetown University Medical Center, Washington, D. C.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director. Hahnemann Medical College, Philadelphia, Pa.

OCT. 10–14 **Vectorcardiography.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

DEC. 8–10 Henry I. Russek, FACC, director. Americana Hotel, New York, N. Y. Title unavailable.

Advance registration forms for these courses may be obtained by writing to Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Continuing Medical Education: Advance Programs

MARCH 20–25, 1972

New York, New York

CONSULTANT'S COURSE IN CARDIOLOGY

Sponsors:

The American College of Cardiology
and
Mount Sinai School of Medicine
of the City University of New York

Program directors:

SIMON DACK, MD, FACC
ARNOLD M. KATZ, MD, FACC
ROBERT S. LITWAK, MD, FACC
New York, New York

This 6-day program will review in depth the newest concepts of cardiac function, diagnosis and therapy. Its aim is to provide the participant with both a review of established knowledge and an exposure to the newest information in basic and clinical cardiology. Presentation of clinical concepts will be based on a thorough grounding in the underlying basic principles. Each day's program will be devoted to 1 subject, led and integrated by a senior member of the faculty. The informal atmosphere of a small group will allow students to participate in discussions of the most important aspects of modern cardiology and will permit meaningful interaction with experts in their fields.

The specific objectives of this program are a complete understanding of the mechanical and electrical bases of cardiac function; correlation of cardiac anatomy and embryology; diagnosis and treatment of cardiac arrhythmias; diagnosis and surgical management of valvular heart disease; and medical and surgical management of myocardial infarction and coronary heart disease. Instruction will be carried out in an informal atmosphere, partly by lectures and partly by group discussions. Students will be presented with problem situations and "unknowns" for discussion, and practical demonstration will be used extensively in the coronary care and cardiac surgical intensive care units.

The program is directed particularly to experienced and newly qualified cardiologists and highly experienced internists.

Local Faculty:

Drs. Murray Baron, Simon Dack, Ephraim A. Donoso, Jacob I. Haft, Arnold M. Katz, Madeline A. Kirschberger, Leslie A. Kuhn, Robert S. Litwak, Salvador B. Lukban, and John Pantazopoulos, Miss Doris I. Repke and Dr. Michihko Tada

Enrollment:

Maximal enrollment for this program is 20. Advance registration is required.

Fee:

ACC members and nonmembers, $250.

APRIL 5–7, 1972

Scottsdale, Arizona

VECTORCARDIOGRAPHY: A WORKSHOP

Sponsors:

The American College of Cardiology
and
The Institute for Cardiovascular Diseases, Good Samaritan Hospital
Phoenix, Arizona

Program director:

ALBERTO BENCHIMOL, MD, FACC
Phoenix, Arizona

This is an intensive 3 day program covering the field of vectorcardiography and related areas. Major emphasis is placed on theoretical and practical applications of the technique as related to the patient's diagnostic problems. Half of the program is dedicated to individual analysis of routine vectorcardiograms by the participants under the orientation of the guest and local faculty. This is an advanced course in vectorcardiography for those physicians who already have a basic understanding of electrocardiography and vectorcardiography and wish a close exposure to the values and limitations of vectorcardiography.

Guest faculty:

Dr. Ronald H. Selvester, Los Angeles, Calif.

Local faculty:

Drs. Jose Baldi and Kenneth B. Desser, Mr. John L. Gartlan, Jr., Drs. John H. Gay, Charles L. Harris, Boh T. Kwee, Kiyoshi Mori, Steven D. Promisloff, Marian E. Molthan, James A. Schumacher and Beatriz F. Valda.

Enrollment:

Enrollment is limited to 60 for this program. Advance registration is required.

Fee:

ACC members, $200; nonmembers, $250.

APRIL 17–20, 1972

Las Vegas, Nevada

CURRENT CONCEPTS IN CARDIOLOGY—1972

Sponsors:

The American College of Cardiology
and
The Cardiovascular Department
Sunrise Hospital
Las Vegas, Nevada

Program director:

PHILIP R. AKRE, MD
Las Vegas, Nevada

Program co-director:

JOHN A. BOWERS, MD
Las Vegas, Nevada

This program is designed to provide for the practicing internist and cardiologist an in-depth presentation of basic concepts of, and recent developments in, the field of cardiology. The meeting will be conducted in the manner of a seminar with each speaker being provided adequate time to permit a thorough discussion of his subjects, with ample opportunity for involvement of participants in the discussion. Two 3-hour sessions will be conducted daily by speakers of national prominence.

Guest Faculty:

Drs. Anthony N. Damato, Staten Island, N. Y.; Charles Fisch, Indianapolis, Ind.; Noble O. Fowler, Cincinnati, Ohio; B. L. Martz, Indianapolis, Ind.; Lawrence E. Meltzer, Philadelphia, Pa.; and F. Mason Sones, Jr., Cleveland, Ohio.

Enrollment:

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Fee:

ACC members, $125; nonmembers, $175.

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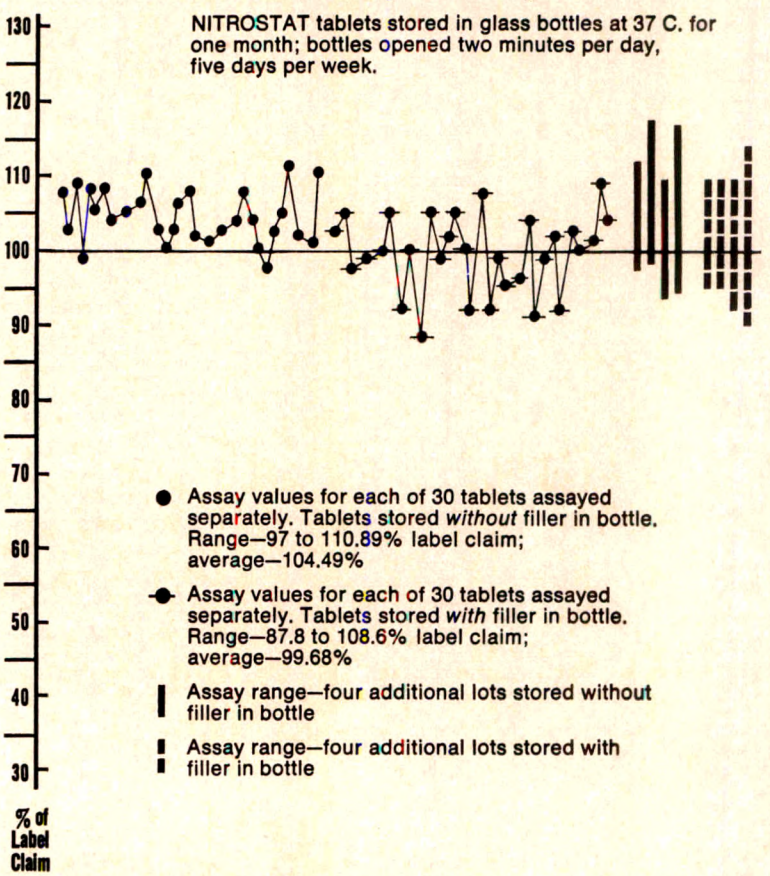

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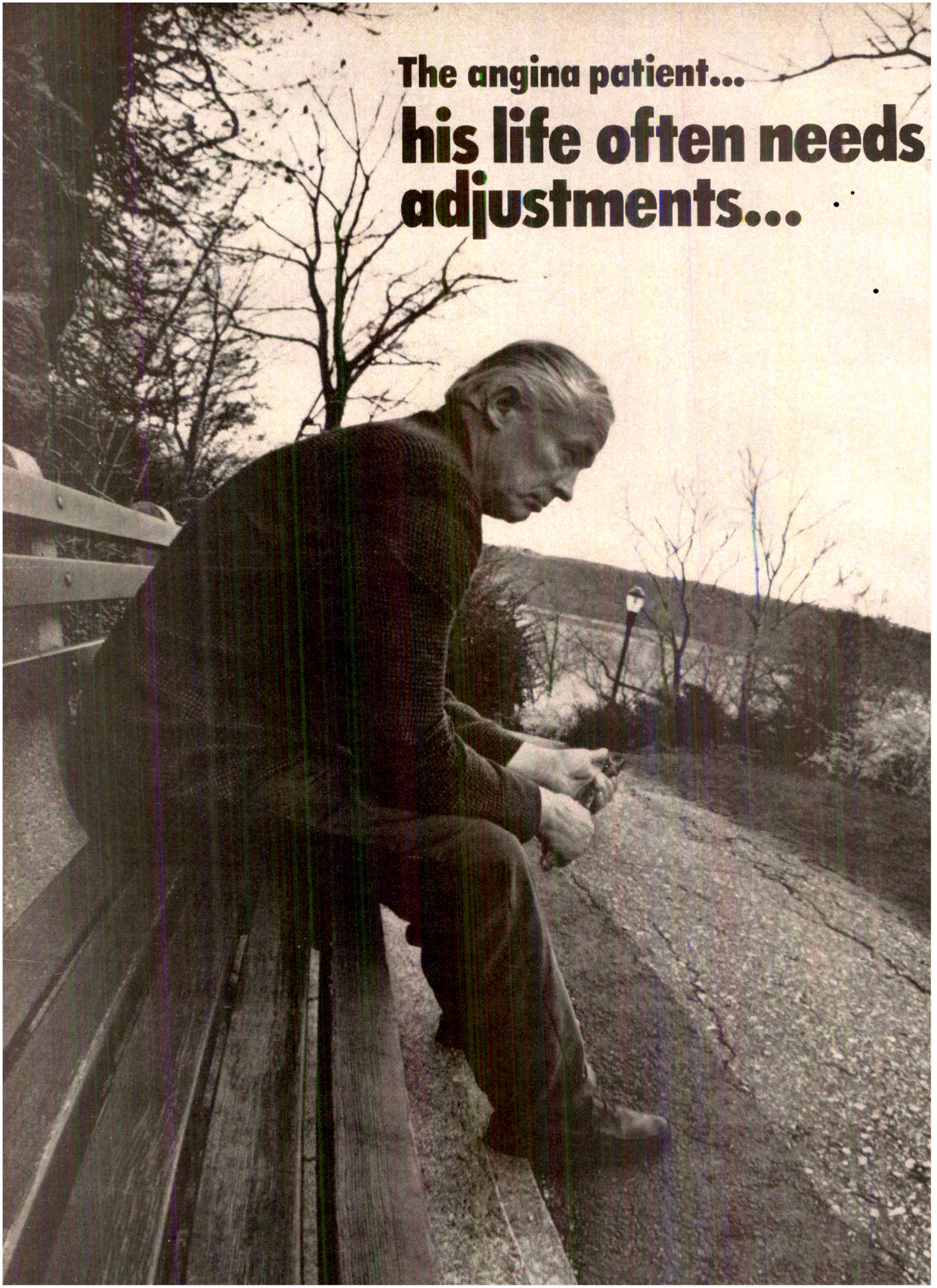
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- **Address manuscript** to Simon Dack, MD, American Journal of Cardiology, 466 Lexington Ave., New York, NY 10017.
- **Submit two copies** of all elements of the article: text, references, legends, tables and figures.
- **Arrange the paper** in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- **Number all pages** in above sequence, beginning with title page as 1, abstract as 2, etc.
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- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

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- **Place acknowledgments** at end of text, before references.

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(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

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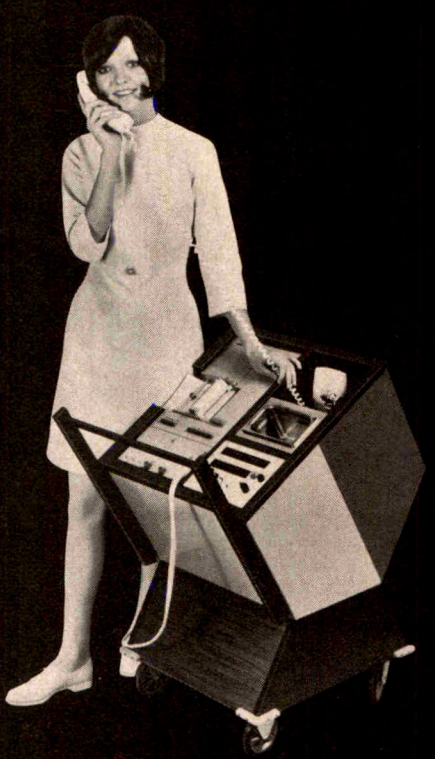

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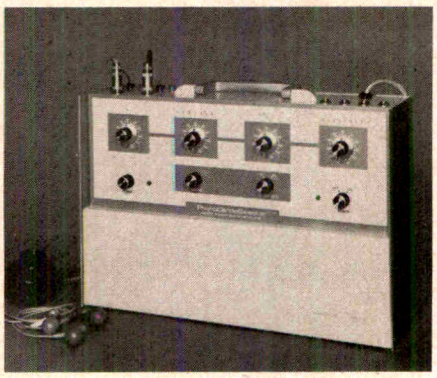

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heart sound diagnostic unit

This instrument enables the physician to listen, independently, or in combination, to the patient's first heart sound (S_1), systolic interval, second heart sound (S_2) or diastolic interval. The amplification of these time zones may be varied independently. And the patient's heart rate can, in effect, be reduced by one-half to permit a more objective interpretation of the sounds.

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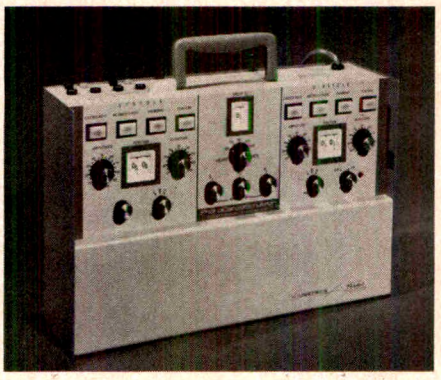

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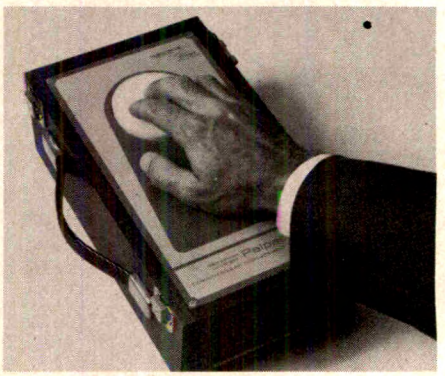

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Circulation

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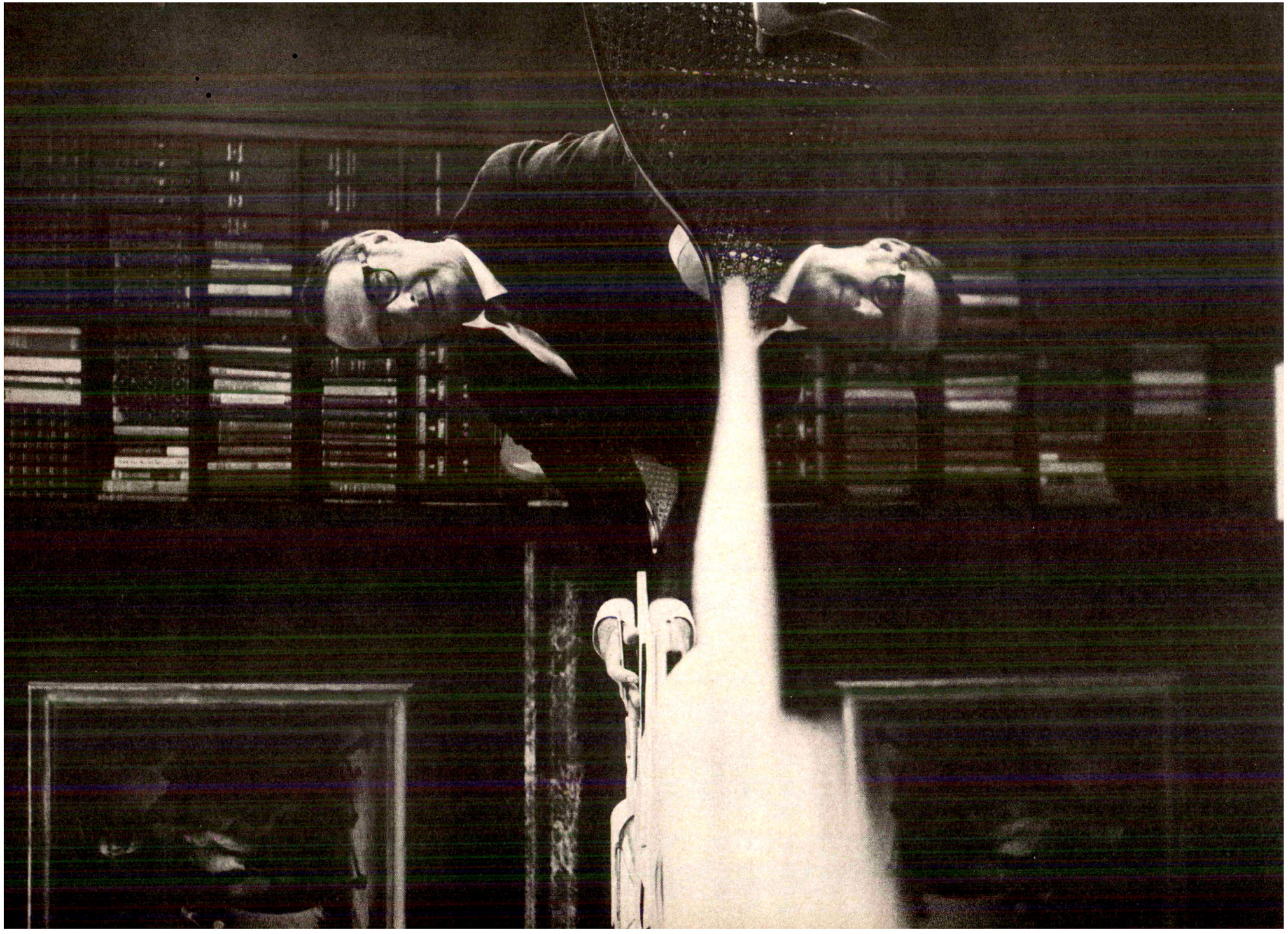

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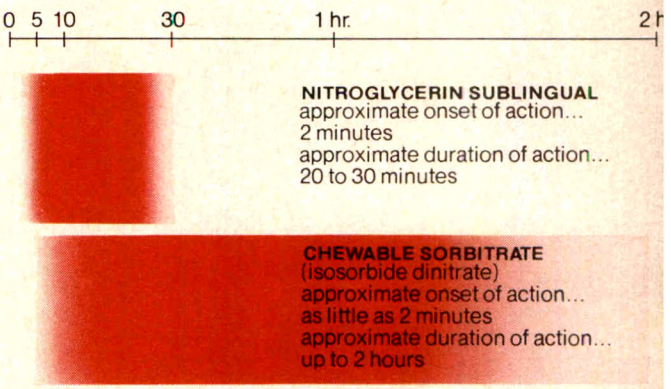

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Mode of Action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: *Sublingual and Chewable:* For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Route:* Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 or 4 times daily. Chewable SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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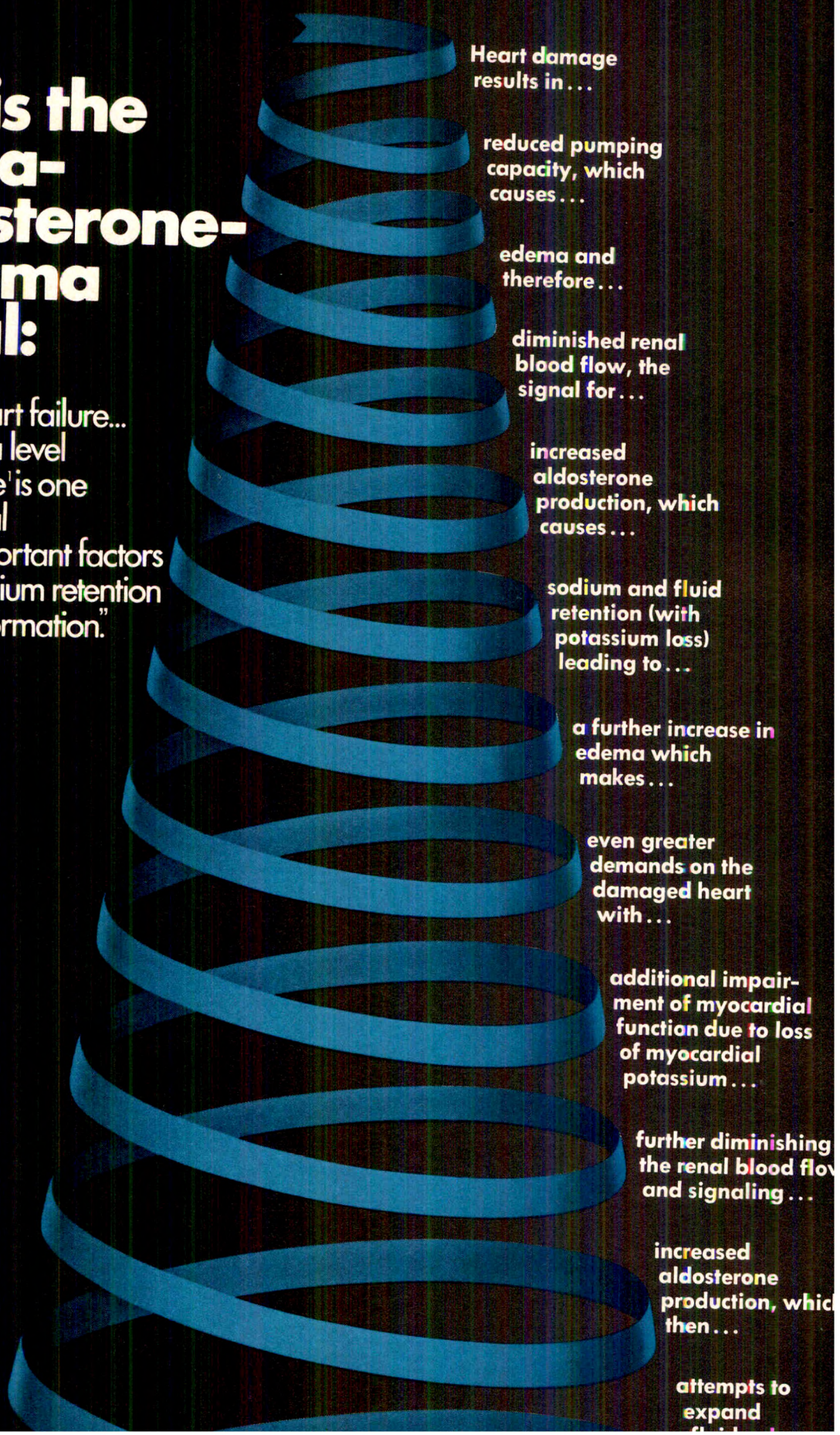

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the only specific, competitive aldosterone antagonist for gradual, sustained diuresis with minimal possibility of potassium loss... especially indicated for the digitalized patient

- Produces a gradual, sustained diuresis which, over a period of weeks, may be greater than that produced[2] with furosemide or ethacrynic acid, while avoiding the dangers of sudden fluid or electrolyte depletion common with fast-acting diuretics.

- Helps prevent digitalis toxicity due to low myocardial potassium levels by helping to retain or restore myocardial potassium through its "...action on the kidney, where it blocks[3] aldosterone action, and perhaps by direct cellular action as well...." In contrast, thiazides, furosemide and ethacrynic acid cause potassium loss which can potentiate[4] myocardial potassium outflow.

- May be combined with other diuretics for an additive effect—permitting lower dosages with each agent while helping to maintain potassium balance.

Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone, particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For **essential hypertension** in **adults** the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For **edema, ascites** or **effusions** in **adults** initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For **children** the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References: 1. Davis, J. O.: Hosp. Pract. **5**:63-76 (Oct.) 1970. **2.** Laragh, J. H.: Hosp. Pract. **5**:43-50 (Nov.) 1970. **3.** Tourniaire, A., and others: Lyon Méd. **223**:707-716 (March 29) 1970. **4.** Seller, R. H.: Quoted in **Medical News** Section, J.A.M.A., **215**:200-201 (Jan. 11) 1971.

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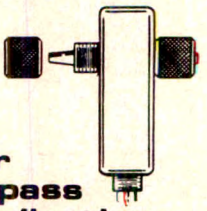

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This course introduces the principles involved in computer analysis of the electrocardiogram and vectorcardiogram in clinical cardiology. The methods and equipment utilized will be demonstrated. This will be followed by a detailed presentation of the results obtained in the recording and interpretation of 1) arrhythmias, 2) normal records, and 3) the various abnormal cardiac conditions, such as LVH, RVH, BBB, myocardial infarction, etc. Automation of the hospital heart station by computer will also be included. Practical considerations concerning comparative and pediatric programs will be discussed. The lecture material will be followed by a work-shop with direct participation by those attending the course. This will be based upon a description booklet which will be provided containing 12 unknown tracings, each followed by computer printouts and clinical data.
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INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. STRICT ATTENTION SHOULD BE PAID TO THE INDICATIONS AND CONTRAINDICATIONS. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS IN EUTHYROID PATIENTS: 1) Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status. 2) Hypertensive states (other than mild, labile systolic hypertension). 3) Advanced liver or kidney disease. 4) Pregnancy. 5) Nursing mothers. 6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; when either or both are present, the advantages of sodium dextrothyroxine therapy must be weighed against the possibility of deleterious results.

WARNINGS: BECAUSE THE EFFECTS OF ANTICOAGULANTS MAY BE POTENTIATED, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY AND READJUST AS NECESSARY ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. CONCENTRATION OF FACTORS VII, VIII, IX, AND PLATELET ACTIVITY SHOULD ALSO BE MONITORED, SINCE THESE FACTORS MAY BE DECREASED. CONSIDER WITHDRAWAL OF CHOLOXIN 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients with cardiac disease is required, and the drug should be withdrawn or dosage reduced if aggravation of angina, increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops. Hypothyroid patients are more sensitive than euthyroid patients, especially if treated concomitantly with other thyroid preparations. Special consideration must be given to the dosage of the hypothyroid patient.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias or coronary insufficiency. Drug withdrawal or careful observation of patients receiving such injections is recommended, especially before elective surgery. In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and subsequent readjustment if dextrothyroxine is later withdrawn.

USAGE IN WOMEN OF CHILDBEARING AGE: Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of Choloxin to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

PRECAUTIONS: Unusually high PBI values are common in treated patients and are not evidence of hypermetabolism. In children, use only when a significant cholesterol-lowering effect is observed. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism and thus more common in the hypothyroid patient, especially the hypothyroid cardiac. Cardiac changes have rarely been precipitated in non-cardiac patients: Angina pectoris (0.2% incidence), arrhythmia (0.5%), myocardial ischemia (<0.1%), cardiomegaly (<0.1%), fatal and non-fatal myocardial infarctions (<0.2%): Insomnia, nervousness, palpitations, tremors, weight loss, lid lag, sweating, flushing, hyperthermia, hair loss, changes in bowel habits, diuresis, and menstrual irregularities may also be related to the metabolic action. A few patients developed itching and skin rashes, apparently from iodism.

Dyspepsia, nausea and vomiting, and changes in appetite occurred in less than 1%. Headache, changes in libido, hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain and bizarre complaints were reported in less than 1% of treated patients. Gallstones were newly discovered in 13 patients, and cholestatic jaundice in one, although relationship to drug therapy was not established. In a total of 19 patients, pre-existing peripheral vascular disease, exophthalmos, retinopathy, and disturbed sensorium continued to worsen. Cerebrovascular accidents, thrombophlebitis, and G.I. hemorrhages each occurred in less than 1% of patients, but there appears to be no relationship to dextrothyroxine therapy.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

DOSAGE RECOMMENDATIONS: For *adult* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is 4.0 to 8.0 mg. per day. The initial daily dose should be 1.0 to 2.0 mg. to be increased in 1.0 or 2.0 mg. increments at intervals of not less than one month to a maximum level of 6.0 to 8.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol. When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients, the more conservative dosage schedule is recommended.

For *pediatric* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is approximately 0.1 mg./kg. The initial daily dosage should be approximately 0.05 mg./kg., to be increased in 0.05 mg./kg. increments at monthly intervals. The recommended maximal dose is 4.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

HOW SUPPLIED: Choloxin brand of sodium dextrothyroxine is supplied in prescription packages of 30 and 100 scored, 2 mg. (yellow) and 4 mg. (white) tablets.

An Important Note: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

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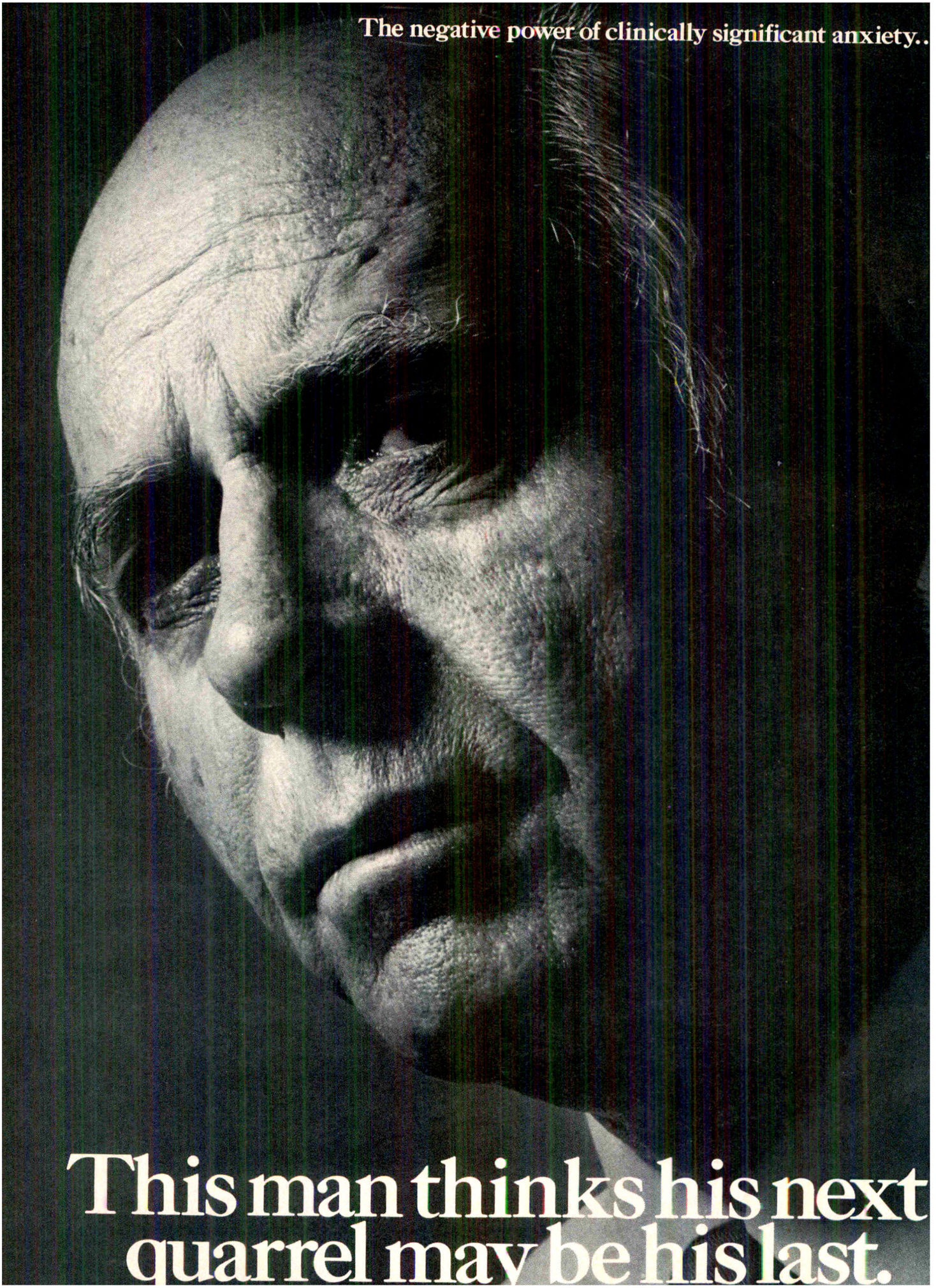
The negative power of clinically significant anxiety..
This man thinks his next quarrel may be his last.

For the hypertensive patient, severe symptoms may be intensified and aggravated by emotional overreaction to stress. Acutely aware of the adverse impact his emotions may have on the course of his life, the hypertensive patient's anxieties may be increased.

Adjunctive use of Libritabs may be of significant value in reducing excessive anxiety, which can induce adverse biochemical and physiological changes related to the vascular system and, by so doing, jeopardize management of the disease itself.

Libritabs (chlordiazepoxide) is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics and antihypertensive agents, whenever anxiety is a significant component of the clinical profile.

Libritabs is especially well suited for extended use because of its wide margin of safety. In general use, the most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated. (See summary of prescribing information.) Moreover, the antianxiety benefits of Libritabs are generally maintained without diminution of effect or need for increase in dosage. When treatment is prolonged, periodic blood counts and liver function tests are advisable.

Libritabs (chlordiazepoxide) permits flexible, individualized therapy through its three oral dosage strengths.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances, syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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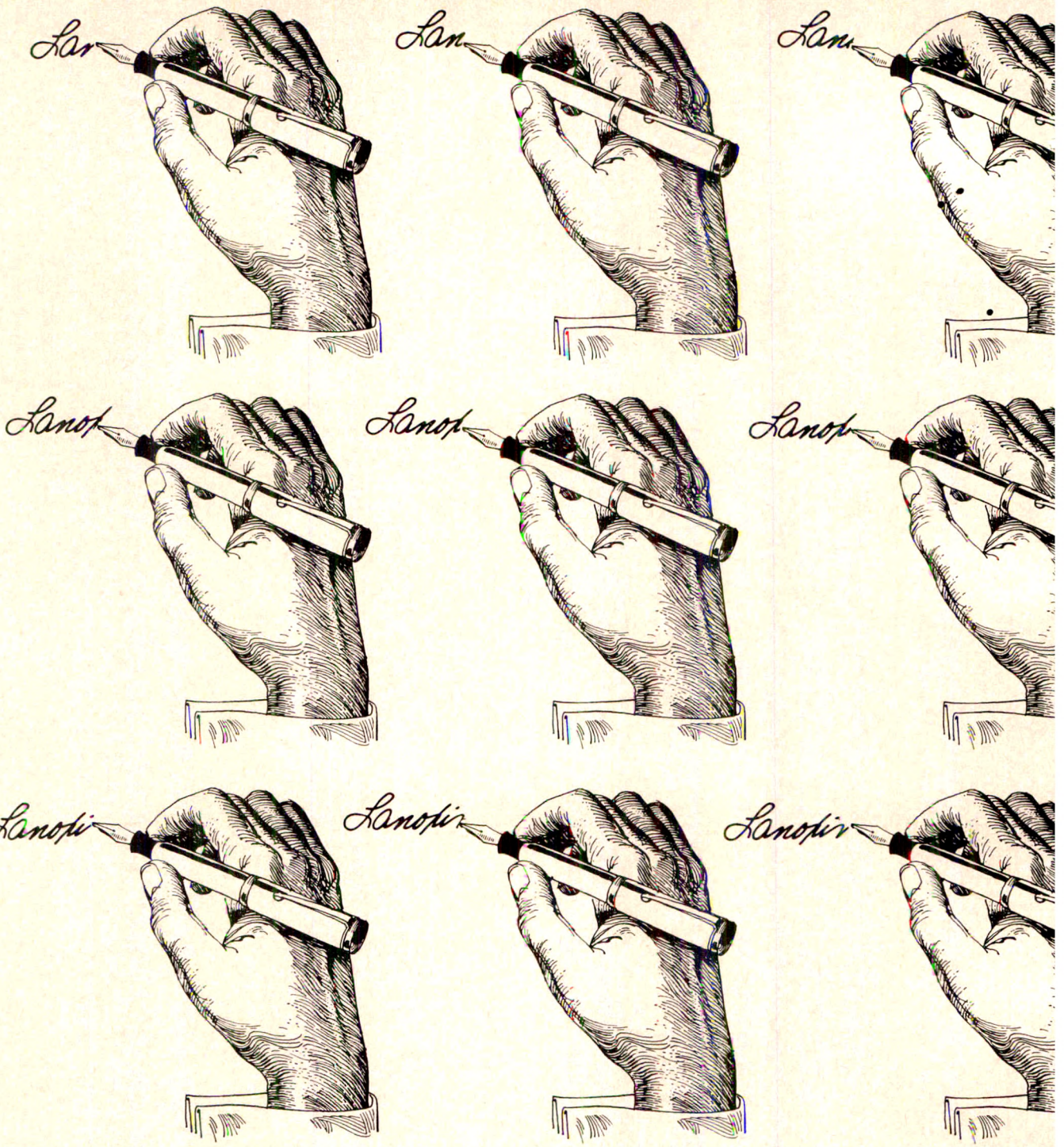

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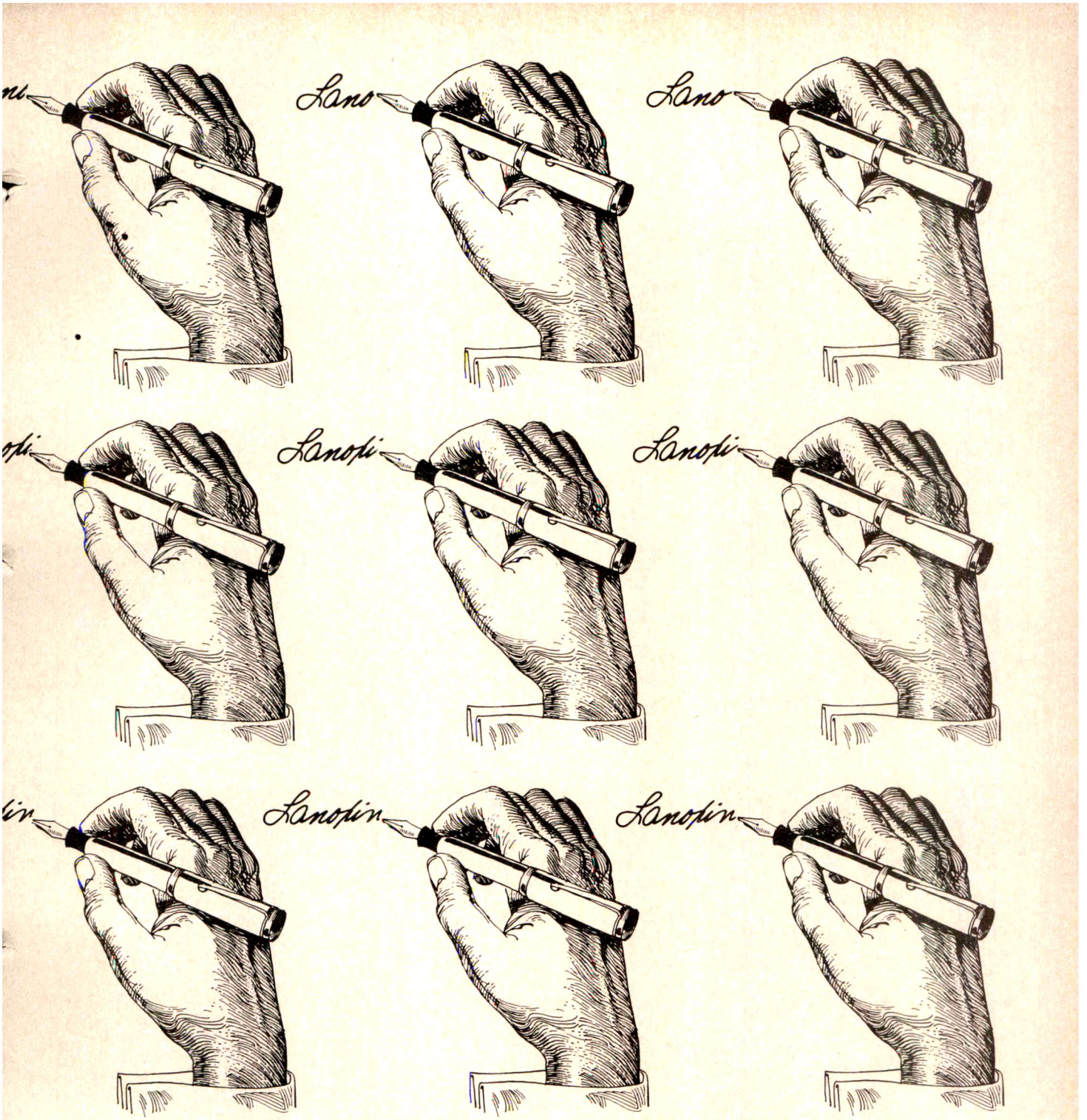
Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used only in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin digoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions it may be necessary to reduce the usual dosages of Lanoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.



Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days. If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl=74.5 mg.) Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

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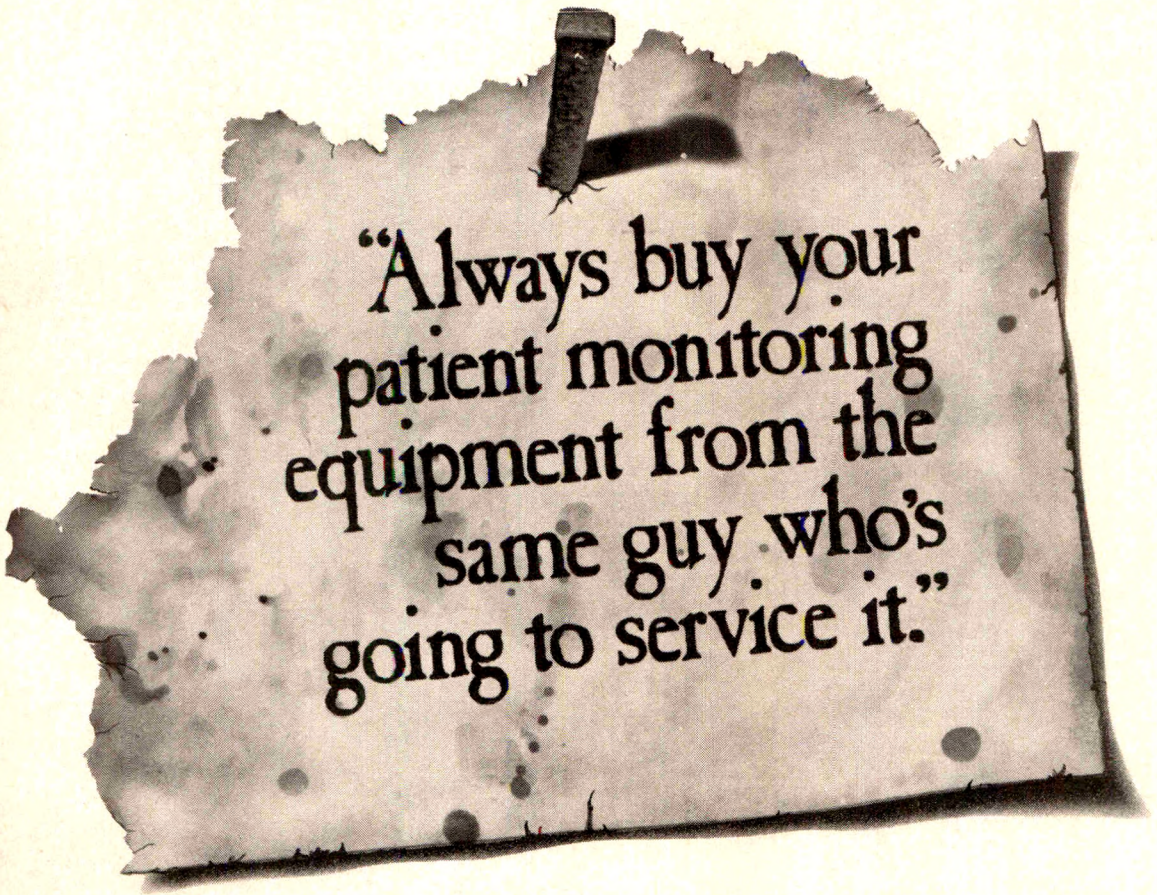

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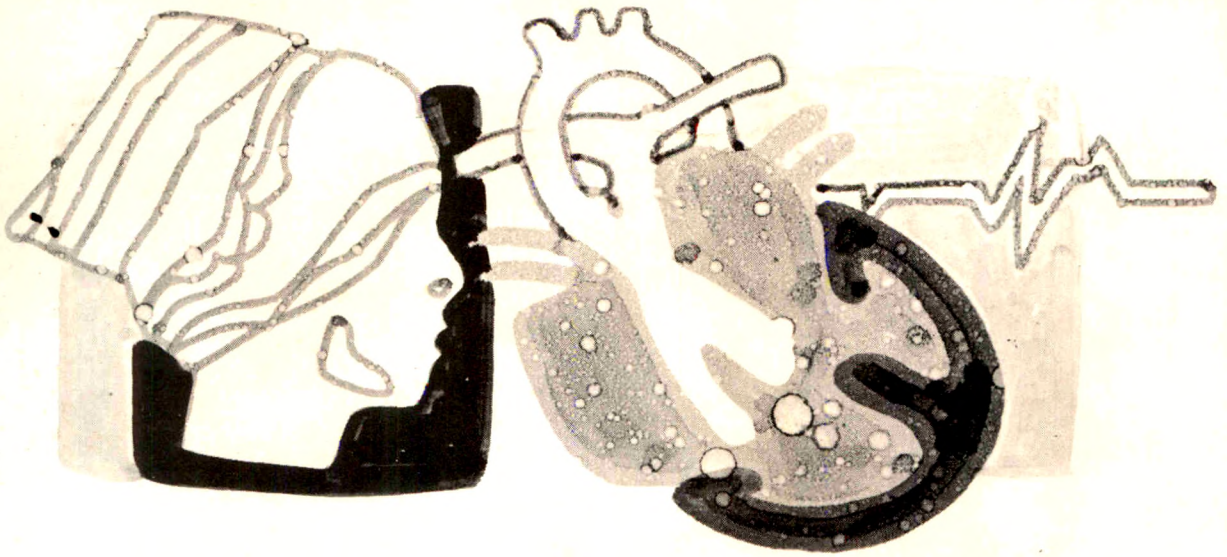

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*Welt, L. G., in Goodman, L. A., and Gilman, A., eds., The Pharmacological Basis of Therapeutics, ed. 3, New York, The MacMillan Co., 1965, p. 790.

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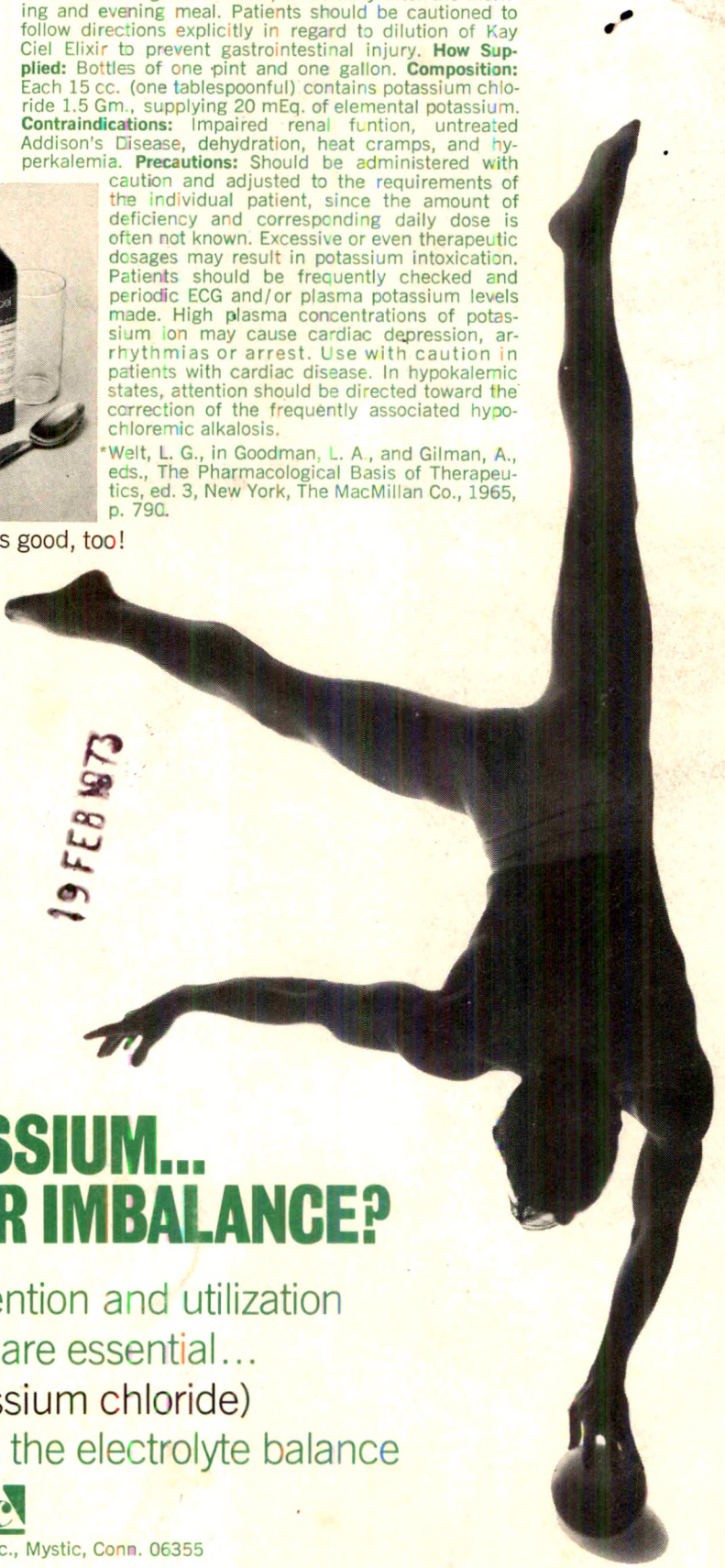

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The most widely used diuretic in cardiac edema

This technique of unwrapping a sphere to make a flat map was invented by Johann Werner, a mathematician who lived at the time of Columbus, long before the exact shape of the New World continents was known. To achieve such an equal-area projection, he kept the central meridian a straight line and intersected it at true distances with parallel lines.

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Lasix®
furosemide Tablets/Injection

WARNING — Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "DOSAGE AND ADMINISTRATION.")

DESCRIPTION — Lasix is a diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by:

- a high degree of efficacy;
- a rapid onset of action;
- a comparatively short duration of action;
- a ratio of minimum to maximum effective dose higher than 1:10;
- the fact that it acts not only at the proximal and distal tubules but also at the ascending limb of Henle's loop.

Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

INDICATIONS — Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

If the gastrointestinal absorption is impaired or oral medication is not practicable for any reason, Lasix is indicated by the intramuscular or intravenous route. The intravenous administration of Lasix is indicated when a rapid onset of the diuresis is desired, e.g., acute pulmonary edema.

Parenteral administration should be reserved for patients where oral medication of Lasix (furosemide) is not practical.

Hypertension — Lasix Tablets may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS — Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities the drug is contraindicated in pregnancy and in nursing mothers.

Lasix is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix is contraindicated in patients with a history of hypersensitivity to this compound.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

WARNINGS — Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium-depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

PRECAUTIONS — As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix is administered, since Lasix potentiates the hypotensive effect of antihypertensive medications.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Cases of reversible deafness and tinnitus have been reported following the injection of Lasix. These adverse reactions occurred when Lasix was injected at doses exceeding several times the usual therapeutic injection dose of 1 to 2 ampules (20 to 40 mg.). Transient deafness is more likely to occur in patients with severe impairment of renal function and in patients who are also receiving drugs known to be ototoxic. Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix, and it is advisable to discontinue oral Lasix for one week and parenteral Lasix two days prior to any elective surgery.

ADVERSE REACTIONS — Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura) may occur. Rare cases of agranulocytosis have occurred which responded to treatment.

Cases of reversible deafness and tinnitus have been reported. These adverse reactions occurred when Lasix Injection was given at doses exceeding several times the usual therapeutic dose of 1 to 2 ampules (20 to 40 mg.). (See "PRECAUTIONS.")

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli (see "WARNINGS"), and acute pancreatitis.

Lasix induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm and symptoms of urinary frequency.

As far as hyperglycemia is concerned, see "PRECAUTIONS."

Transient pain after intramuscular injection has been reported at the injection site.

DOSAGE AND ADMINISTRATION

Oral Administration — The usual dose of Lasix is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). The dose of Lasix may be carefully titrated up to 600 mg. per day in those patients with severe clinical edematous states. Higher doses are currently under investigation.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension — The usual dose of Lasix (furosemide) is one tablet (40 mg.) twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

The dosage of other agents must be reduced by at least 50 per cent as soon as Lasix is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if one tablet (40 mg.) twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

Parenteral Administration — The usual dose of Lasix is 1 to 2 ampules (20 to 40 mg.) given as a single dose, injected intramuscularly or intravenously. The intravenous injection should be given slowly (1 to 2 minutes). Ordinarily, a prompt diuresis ensues. Depending on the patient's response a second dose can be administered two hours after the first dose or later.

If the diuretic response with a single dose of 1 to 2 ampules (20 to 40 mg.) is not satisfactory, e.g., in a patient refractory to maximal doses of thiazides, the following schedule should be used under careful medical supervision: Increase this dose by increments of 1 ampule (20 mg.) not sooner than two hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. Parenteral administration should be reserved for patients where oral medication is not practical. Parenteral therapy with Lasix can be replaced by treatment with Lasix Tablets as soon as this is practical for continued mobilization of edema.

Acute Pulmonary Edema — Since the diuresis evoked by Lasix given intravenously commences within five minutes and leads to an intensive diuresis, the treatment of patients with acute pulmonary edema with Lasix (furosemide) intravenously has proven particularly valuable.

The following schedule is recommended: 2 ampules (40 mg.) of Lasix are to be slowly injected intravenously immediately. Then this dose should be followed by another 2 ampules (40 mg.) one to one and one-half hours later if that is indicated by the patient's condition.

If deemed necessary, additional therapy (e.g., digitalis, oxygen) can be administered concomitantly.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

How Supplied—Lasix Tablets are supplied in white, monogrammed, scored tablets of 40 mg. in amber bottles of 100(FSN 6505-062-3336), 500, and Unit Dose 100's (20 strips of 5). **Lasix Injection** is supplied as a sterile solution in 2 cc. amber ampules containing 20 mg. (with sodium chloride for isotonicity and sodium hydroxide to make the solution slightly alkaline); in boxes of 5 (FSN 6505-435-0377) and 50.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

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In a double-blind study of 342 postop patients, circulatory depression occurred in 13.2% of 174 patients receiving morphine; in 5.4% of 168 patients receiving Talwin.[1]

. . . and in other patients: less respiratory and circulatory depression with Talwin

In a double-blind study of 3 narcotic analgesics and Talwin in 118* patients with suspected acute myocardial infarction, Talwin caused a significantly lower incidence in the fall of systolic blood pressure than the 3 narcotics when the initial pressure was 120 mm. Hg or higher. Unlike the narcotics, Talwin caused a statistically significant *rise* in the systolic blood pressure of patients with initial pressures of less than 120.[2]

In a study of a series of patients given Talwin or meperidine while anesthetized for surgery, the investigators concluded: "It would therefore appear that pentazocine is a much safer drug in respect of respiratory depression than pethidine [meperidine], particularly when repeated injections are to be given, e.g., postoperatively or in obstetric practice."[3]

. . . and less of other adverse effects associated with narcotic analgesics

Compared to morphine, Talwin is relatively free from urinary retention and constipation.

Is less likely to cause nausea, vomiting and diaphoresis than meperidine.

See next page for a complete discussion of adverse reactions and a brief summary of other Prescribing Information.

available in 3 dosage strengths—all within the range of recommended dosage

Talwin is available in 30 mg., 45 mg., and 60 mg. strengths to provide analgesia specific to patients' needs throughout the course of therapy. Most studies indicate that the higher dosage strengths produce little, if any, increase in the incidence of adverse reactions.

References: 1. Wallace, George: *Int. Surg. 53*:135, Feb. 1970.
2. Scott, M. E. and Orr, Rosemary: *Lancet 1*:1065, May 31, 1969.
3. Davie, I. *et al.*: *Brit. J. Anaesth. 42*:113, Feb. 1970.

*Other drugs studied: diamorphine and methadone.

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- **not subject to narcotic controls**

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor. Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, nodules and ulceration at injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.),* each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. Boxes of 10, 25, and 100.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide.

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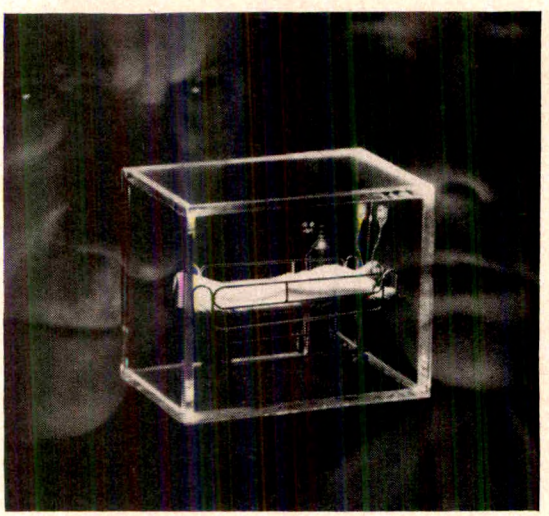

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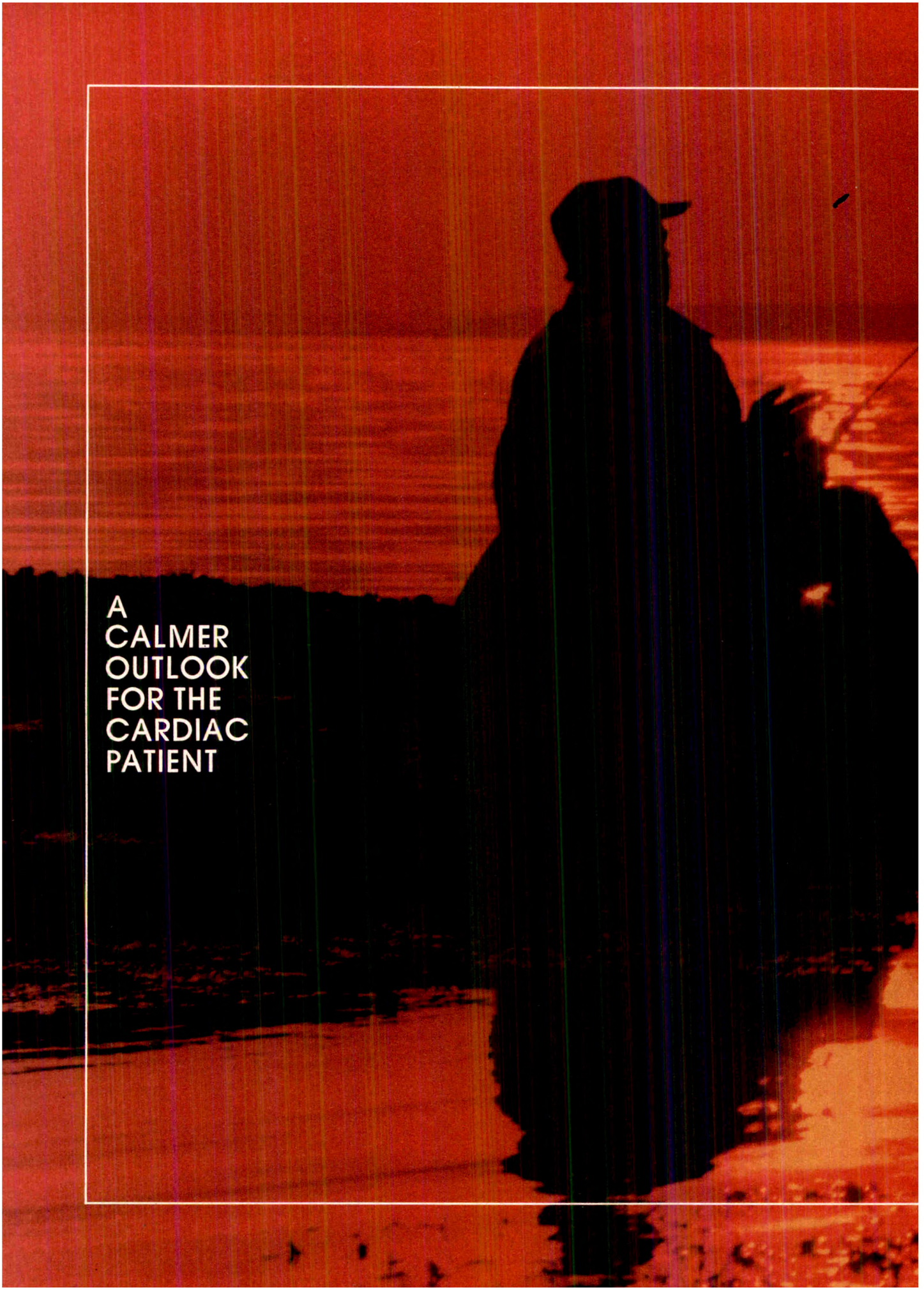
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Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

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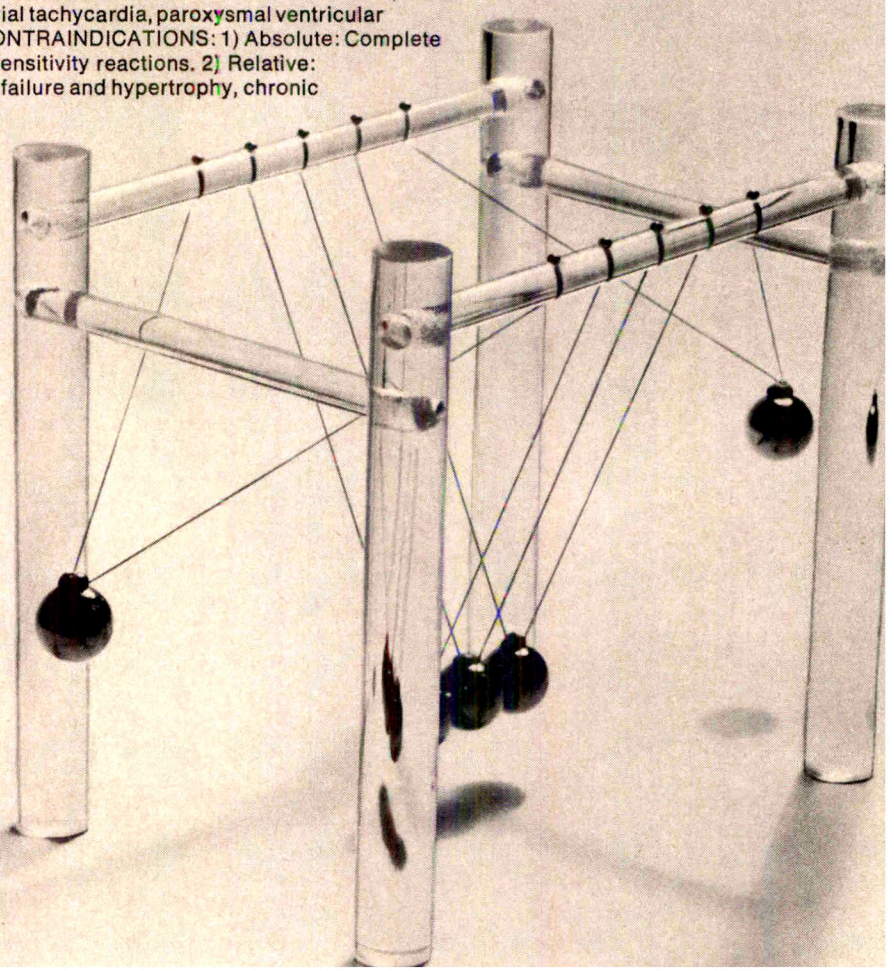

Alone among antiarrhythmics...

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LAWRENCE D. HORWITZ, MICHAEL V. HERMAN and RICHARD GORLIN

Correlation of the clinical response to nitroglycerin with the results of coronary angiography in 70 patients with chest pain of the anginal type discloses that 90 percent of the patients with chest pain relieved within 3 minutes of taking nitroglycerin have coronary artery disease. A delayed or absent response indicates either no coronary artery disease or unusually severe coronary artery disease and angina.

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WILLIAM B. KANNEL and MANNING FEINLEIB

Study of 303 cases of angina in a general population sample of 5,127 persons indicates a poor prognosis for men. One in 4 men with angina can expect to have a coronary attack within 5 years; the risk is half that for women. About 30 percent of patients over age 55 years will die within 8 years, and 44 percent of the coronary deaths will be sudden. Survival in men with uncomplicated angina is no better than that which follows an infarction.

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JOSEPH HILSENRATH, ROBERT I. HAMBY, EPHRAIM GLASSMAN and IRWIN HOFFMAN

This provocative study illustrates the unreliability of predicting coronary obstruction from electrocardiographic and vectorcardiographic patterns of anterior wall infarction, particularly in patients with valvular lesions or primary myocardial disease. Coronary cineangiograms disclosed normal coronary arteries in 53 percent of 60 patients with electrocardiographic and vectorcardiographic evidence of anterior wall myocardial infarction. Triple vessel disease is most commonly present when the criteria for anterior and inferior infarction are met.

171 Clinically Suspect Ischemic Heart Disease Not Corroborated by Demonstrable Coronary Artery Disease. Physiologic Investigations and Clinical Course

WILLIAM A. NEILL, MELVIN P. JUDKINS, DHARAM S. DHINDSA, JAMES METCALFE, DONALD G. KASSEBAUM and FRANK E. KLOSTER

Eleven patients with episodic chest pain resembling angina pectoris and electrocardiographic abnormalities of myocardial ischemia were found to have normal coronary arteriograms and rarely clinical evidence of myocardial hypoxia. Although a conclusive explanation for this unusual syndrome is not currently available, the evidence indicates that these patients manifest a benign course without serious progression of their heart disease.

continued

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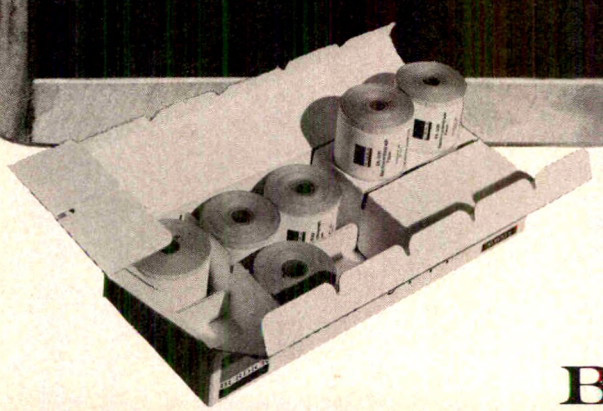

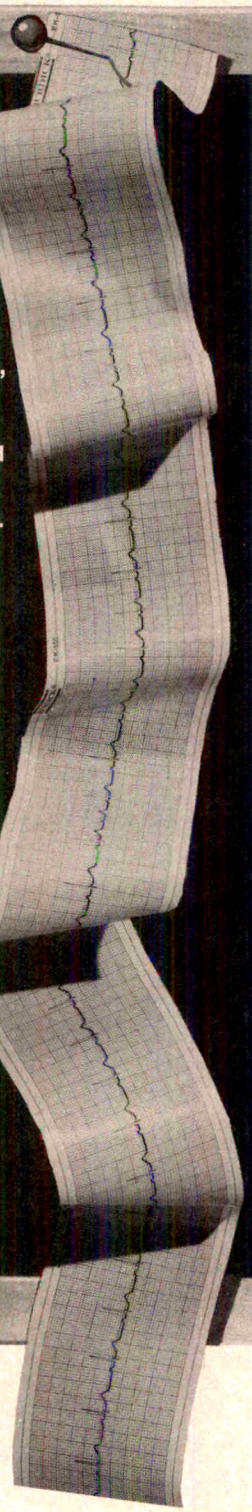

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180 Follow-Up Results of Distal Coronary Artery Bypass for Ischemic Heart Disease

GEORGE C. MORRIS, Jr., GEORGE J. REUL, JIMMY F. HOWELL, E. STANLEY CRAWFORD, DON W. CHAPMAN, H. LISTON BEAZLEY, WILLIAM L. WINTERS, PAUL K. PETERSON and JOHN M. LEWIS

This critical analysis of the clinical state of 480 patients 1 to 30 months after coronary artery bypass shows a 30 day hospital mortality of 6.2 percent, significant improvement in 92 percent of the patients and no degenerative changes in the autogenous vein bypass grafts. Graft occlusions varying from 11 to 14 percent occurred early and were generally due to technical reasons. However, arteriographic studies showed at least 1 functioning graft in 99 percent of patients.

186 Open Heart Surgery for Acquired Heart Disease in Jehovah's Witnesses. A Report of 42 Operations

JOHN R. ZAORSKI, GRADY L. HALLMAN and DENTON A. COOLEY

Favorable results of 42 open heart operations for acquired heart disease in 40 Jehovah's Witnesses testify that blood transfusions can and should be used sparingly to reduce morbidity and mortality in all patients. In this series, with use of a bloodless prime technique of extracorporeal circulation and only brief periods of cardiopulmonary bypass, 3 patients died, anemia causing only 1 death.

190 Hypoplastic Left Heart Syndrome. Clinicopathologic and Hemodynamic Correlation

ABRAHAM SAIED and GORDON M. FOLGER, Jr.

The clinical appearance of 11 patients with the hypoplastic left heart syndrome correlated positively with hemodynamic findings and aided selection for palliative surgery. Group I patients showed elevated values for oxygen saturation in the right heart chambers, pulmonary to systemic flow ratios consistently greater than 1 and right ventricular and pulmonary arterial systolic pressure less than 75 mm Hg. These patients manifested early distress, ashen cyanosis, feeble or absent peripheral pulses in the presence of hyperdynamic precordium and death in the first week of life. Group II, patients with good peripheral pulses, marked cyanosis and survival for more than 1 week, showed low values for right-sided and systemic oxygen saturation, a pulmonary to systemic flow ratio less than 1, and right ventricular and pulmonary systolic arterial pressure greater than 75 mm Hg.

EXPERIMENTAL STUDIES

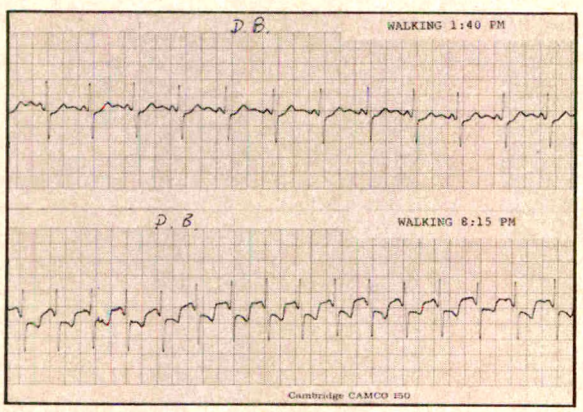
199 Dynamics of Potassium Flux in Cardiac Arrhythmias

T. W. LANG, ELIOT CORDAY, JOSE R. LOZANO, HUGO CARRASCO and SAMUEL MEERBAUM

During rapid ventricular tachycardias in dogs there was a significant net myocardial potassium loss which was associated with more serious arrhythmias leading to resistant ventricular fibrillation. Correction of myocardial potassium balance may be clinically useful in the management of cardiac arrhythmias.

continued

Holter DCG Monitoring Case History No. 19



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JOHN W. LISTER, STEPHEN J. GULOTTA, J. WALTER KELLER, Jr., ALFRED L. ARONSON, PETER TARJAN, DAVID NATHAN and ARTHUR GOSSELIN

Induction of atrial fibrillation by alternating current stimulation of the right atrium proved to be a safe and effective means of terminating supraventricular tachycardia in 6 patients. Slowing of the ventricular rate, after induction of atrial fibrillation, provided a useful means of judging the need for further administration of digitalis.

213 Unidirectional Intraaortic Balloon Pumping in Cardiogenic Shock and Intractable Left Ventricular Failure

ROBERT H. GOETZ, DAVID BREGMAN, BARRY ESRIG and SHLOMO LANIADO

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223 Precordial S–T Segment Elevation Mapping: An Atraumatic Method for Assessing Alterations in the Extent of Myocardial Ischemic Injury. The Effects of Pharmacologic and Hemodynamic Interventions

PETER R. MAROKO, PETER LIBBY, JAMES W. COVELL, BURTON E. SOBEL, JOHN ROSS, Jr. and EUGENE BRAUNWALD

A noninvasive precordial mapping technique using a 15 to 35 electrode blanket to record precordial electrocardiograms in dogs and in human beings provided accurate and reproducible data for evaluating the size of the zone of ischemic injury. This method appears to make it possible to determine the effects of alterations of the hemodynamic state or of pharmacologic agents on the extent and severity of such injury and to assess at the patient's bedside effects of different modes of treatment on the ischemic zone.

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231 The Role of Viruses in the Production of Heart Disease

GEORGE E. BURCH and THOMAS D. GILES

Clinical and experimental data indicate that viruses play an important role in the production of heart disease in man. Viral myocarditis, viral endocarditis, viral pericarditis and viral pancarditis are shown to be true entities. Viruses may be involved in the production of chronic heart disease, cardiomyopathy and "rheumatic heart disease" of undetermined origin. The role of rubella and Coxsackie viruses in congenital heart disease is emphasized, with the suggestion that viral infection acquired in utero may produce heart disease later in life. Measures for prevention of viral heart disease and methods of treatment are reviewed.

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WILLIAM GANZ and H. J. C. SWAN

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SAUL JARCHO

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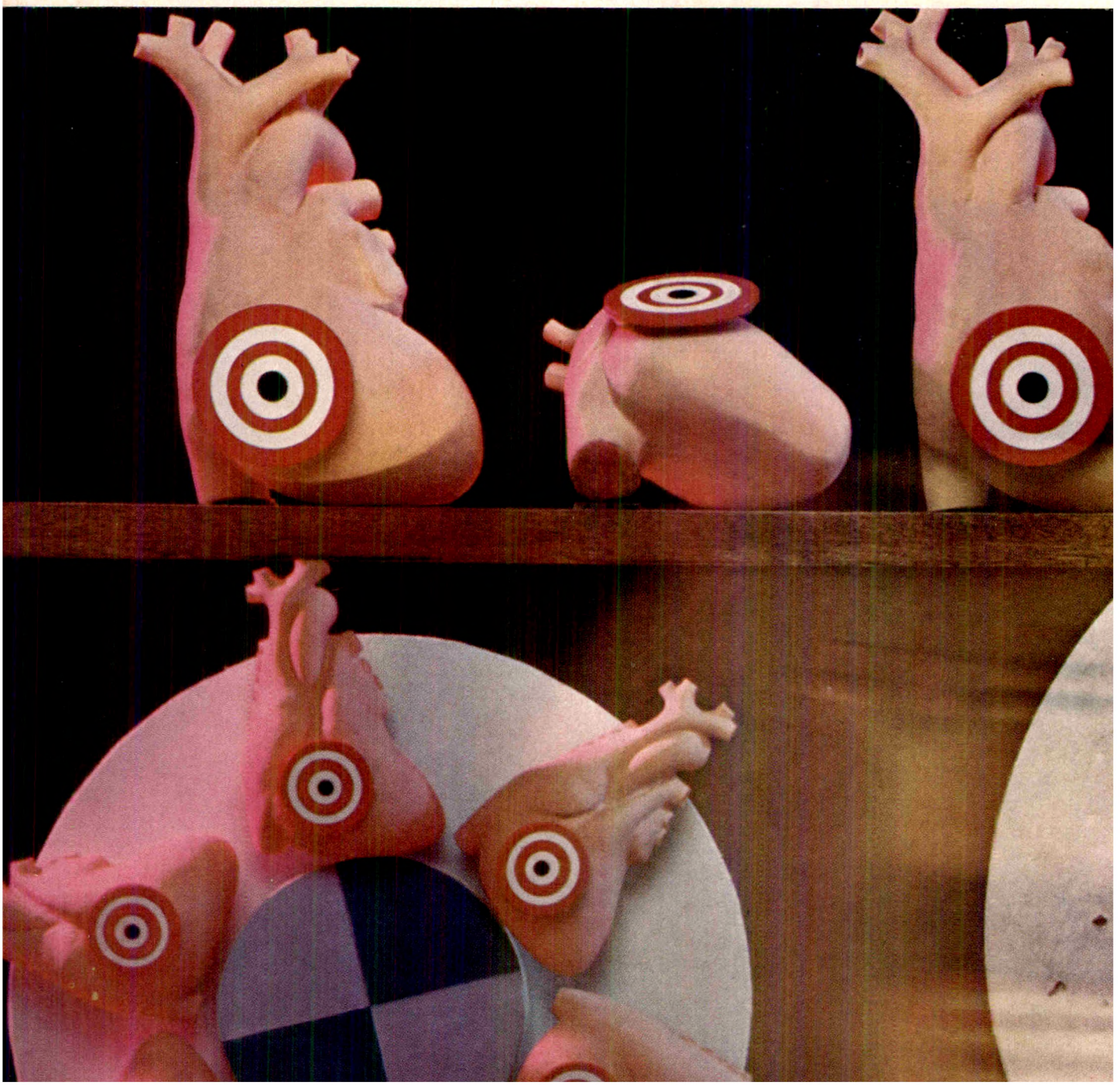

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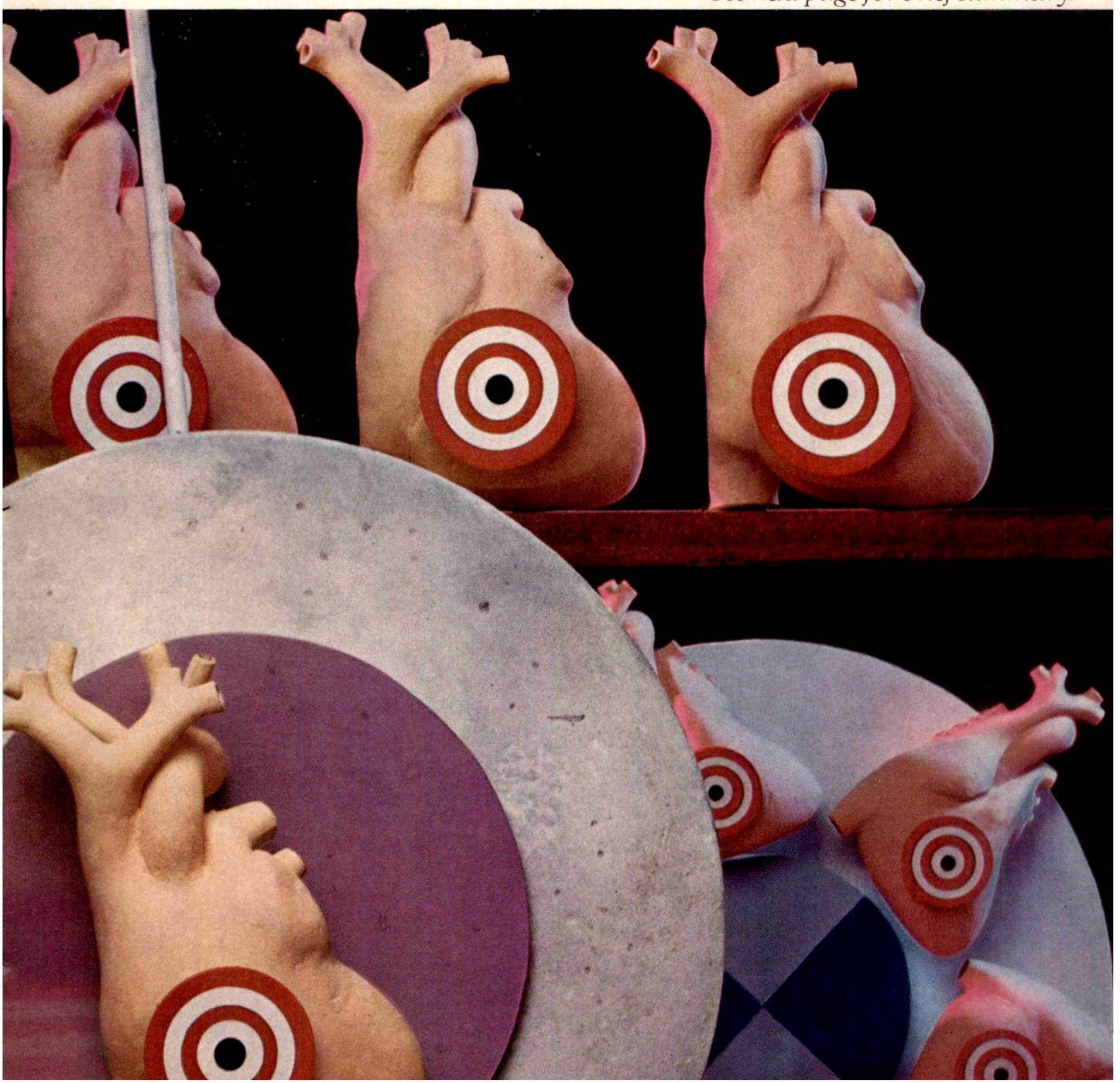

Pronestyl® (Procainamide Hydrochloride) Capsules & Injection zeroes in on ventricular arrhythmias

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 Gm. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. If any sign of lupus erythematosus occurs, LE cell tests should be performed; if cell tests are positive, discontinue drug. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide. Tests at regular intervals for lupus erythematosus are recommended for patients on maintenance therapy.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

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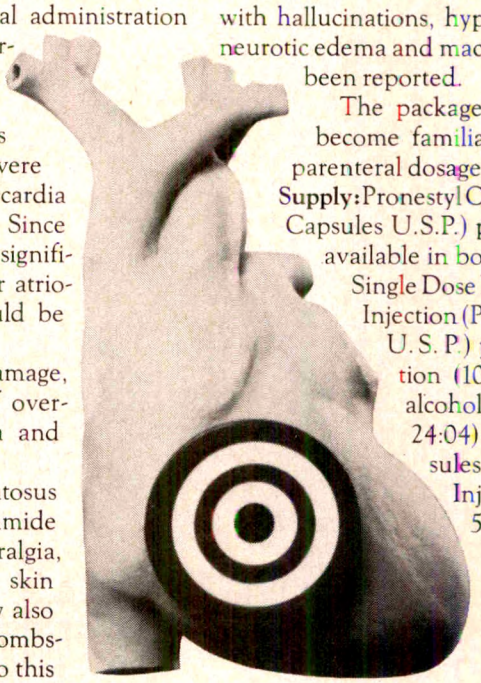

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*Report of Inter-Society Commission for Heart Disease Resources: Primary Prevention of the Atherosclerotic Diseases, Circulation 42:55-95, Dec. 1970.

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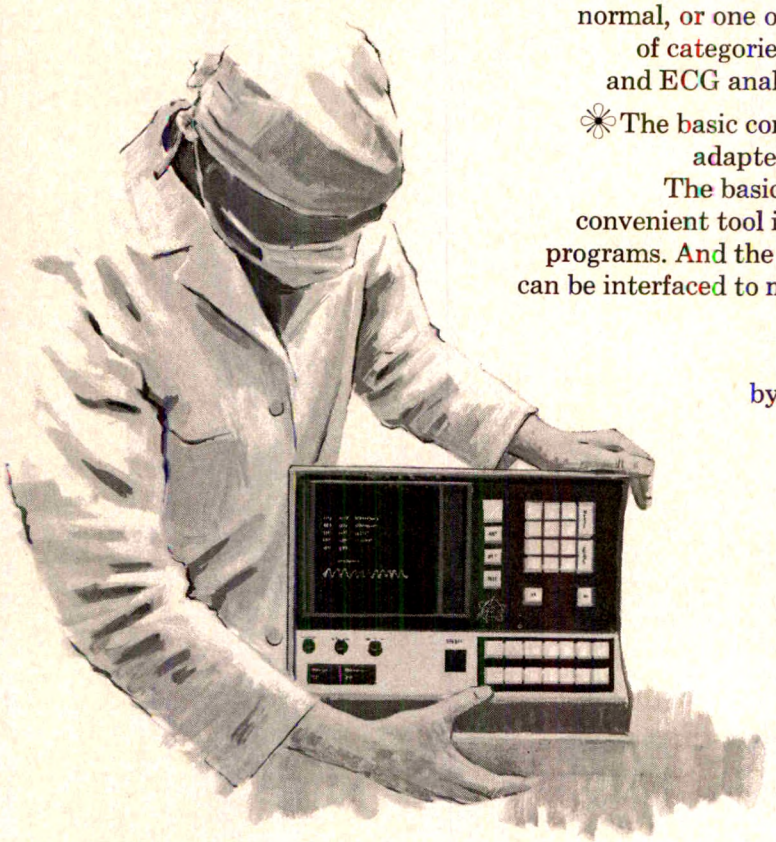

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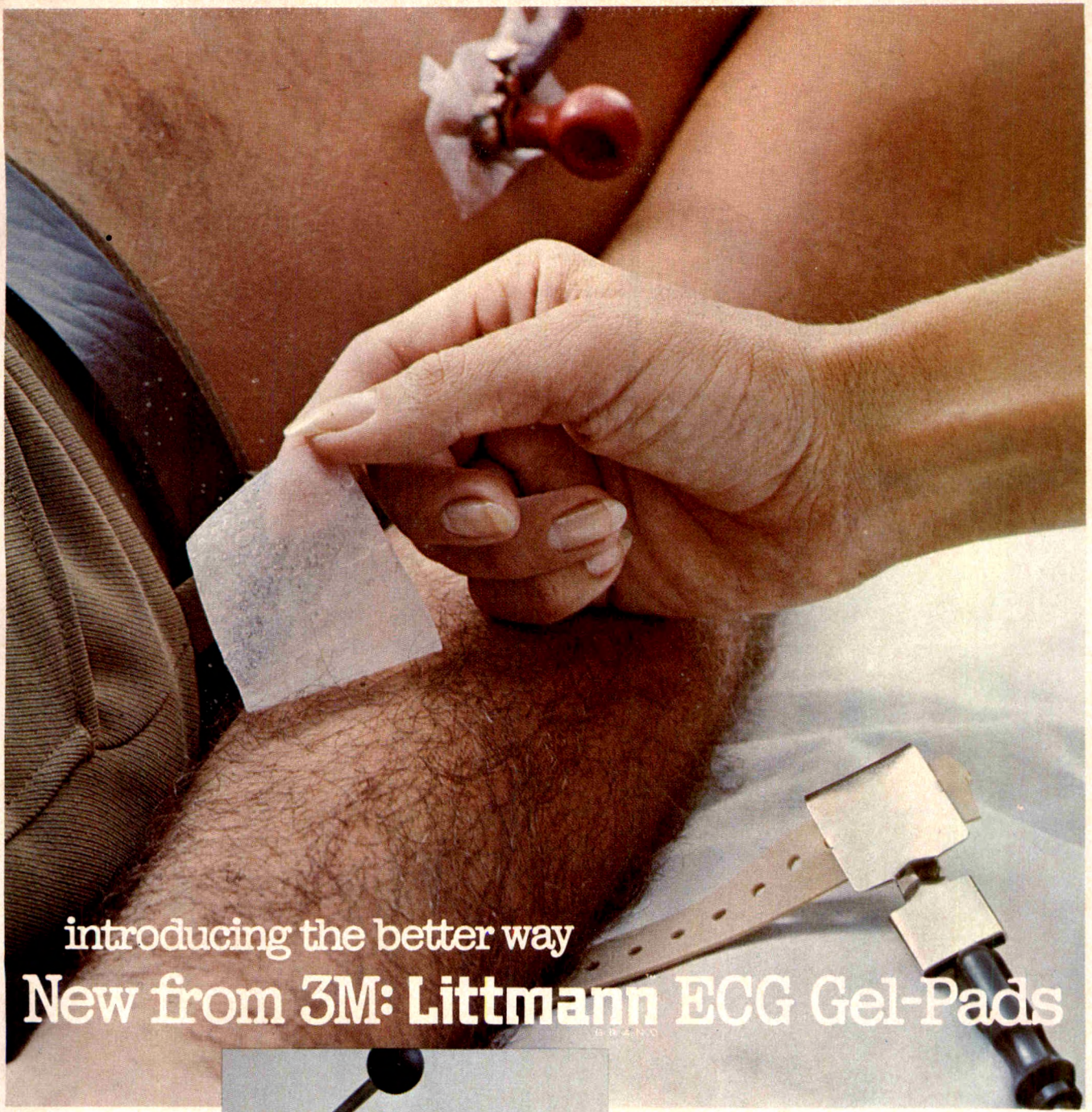

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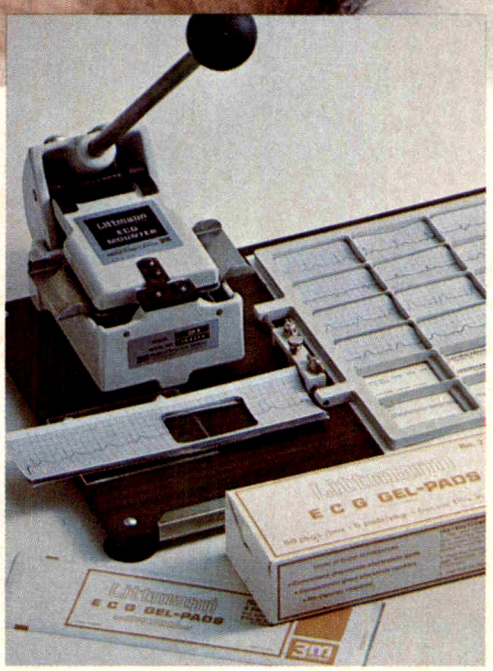

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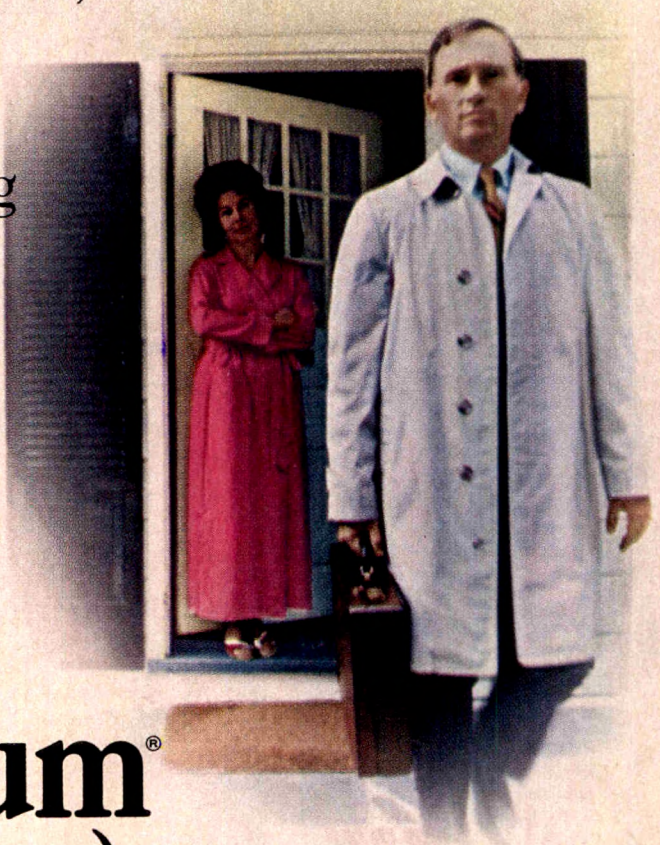

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If the cardiac patient has nighttime psychic tension, an *h.s.* dose added to the *t.i.d.* schedule can ensure a restful night's sleep.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg tablets

When the tense cardiac patient must be kept calm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation, or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect: *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose™ packages of 1000.

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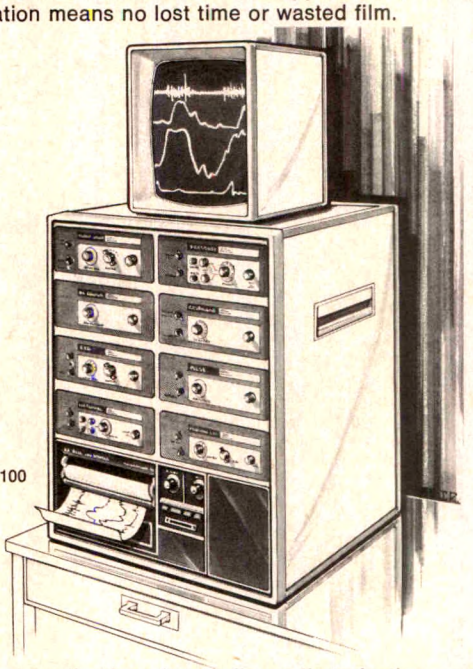

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IS A DIURETIC MAKING A MONKEY OUT OF HER?

Potassium deficit is a common complication of therapy with most diuretics.[1] Provided the patient is willing to eat large quantities of potassium-rich foods (for example, **half a dozen bananas daily**),[2] it is possible to restore her potassium reserves from dietary sources alone. In most instances, however, it simply is **not** feasible to eat away a potassium deficit[3]—all the more reason for prescribing a diuretic which stops potassium depletion **before** it starts....

Effectiveness	Comparable to plain hydrochlorothiazide[4]
Potassium-Sparing Effect	Potassium supplementation virtually unnecessary[5]
Continuing Control	Does not lose effectiveness in presence of aldosterone buildup[6]
Edema Mobilization	Smooth onset of action[7]
Patient Comfort	Minimizes chance of muscle weakness, leg cramps, and fatigue from potassium depletion[8]
Economy	Cost is comparable to plain thiazides, dose for dose

TAKE A SECOND LOOK— 'DYAZIDE' CAN STOP POTASSIUM DEPLETION BEFORE IT STARTS, WITH NO SACRIFICE OF THIAZIDE EFFECTIVENESS...

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Trademark

Dosage in Edema: The usual starting dosage is one capsule twice daily after meals. The usual maintenance dosage is one capsule daily or every other day. The maximum daily dosage should not exceed one capsule four times daily.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; its potential benefits should be weighed against possible hazards to the fetus.

See next page for indications and brief prescribing information.

Before prescribing, see complete prescribing information in SK&F literature or PDR.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome, late pregnancy; also steroid-induced and idiopathic edema, and edema resistant to other diuretic therapy. 'Dyazide' is also indicated in the treatment of mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., certain elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—they can both cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules.

SK&F Co., Carolina, P.R. 00630
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References:

1. Wilson, G.M.: Diuretics, Practitioner *200:*39 (Jan.) 1968.
2. Westerman, R.L., and Snively, W.D., Jr.: Potassium Deficit: Clinical Aspects, GP *33(6):*85 (June) 1966.
3. Lyon, A.F., and DeGraff, A.C.: Metabolic Complications of Thiazide Therapy and Their Correction. Am. Heart J. *68:*710 (Nov.) 1964.
4. Brest, A.N.: Refractory Heart Failure, GP *33(2):*99 (Feb.) 1966.
5. Cattell, W.R., and Havard, C.W.H.: Diuretic Action of Triamterene in Man, Brit. M.J. *2:*1362 (Nov.) 1962.
6. Seller, R.H., et al.: Aldosterone Antagonists in Diuretic Therapy, Arch. Int. Med. *113:*350 (March) 1964.
7. Tannenbaum, P.J.; Crosley, A.P., and Free, S.M.: Unpublished Study—data available from SK&F Medical Dept., Phila., Pa. 19101.
8. Heath, W.C., and Freis, E.D.: Triamterene with Hydrochlorothiazide in the Treatment of Hypertension, J.A.M.A. *186:*119 (Oct. 12) 1963.

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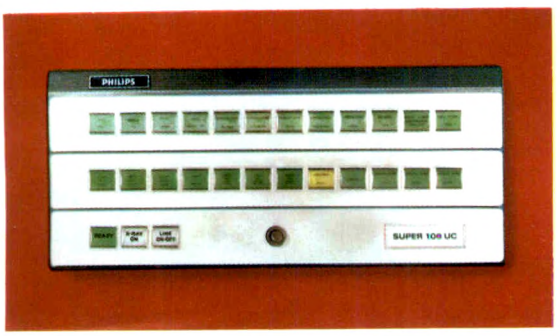

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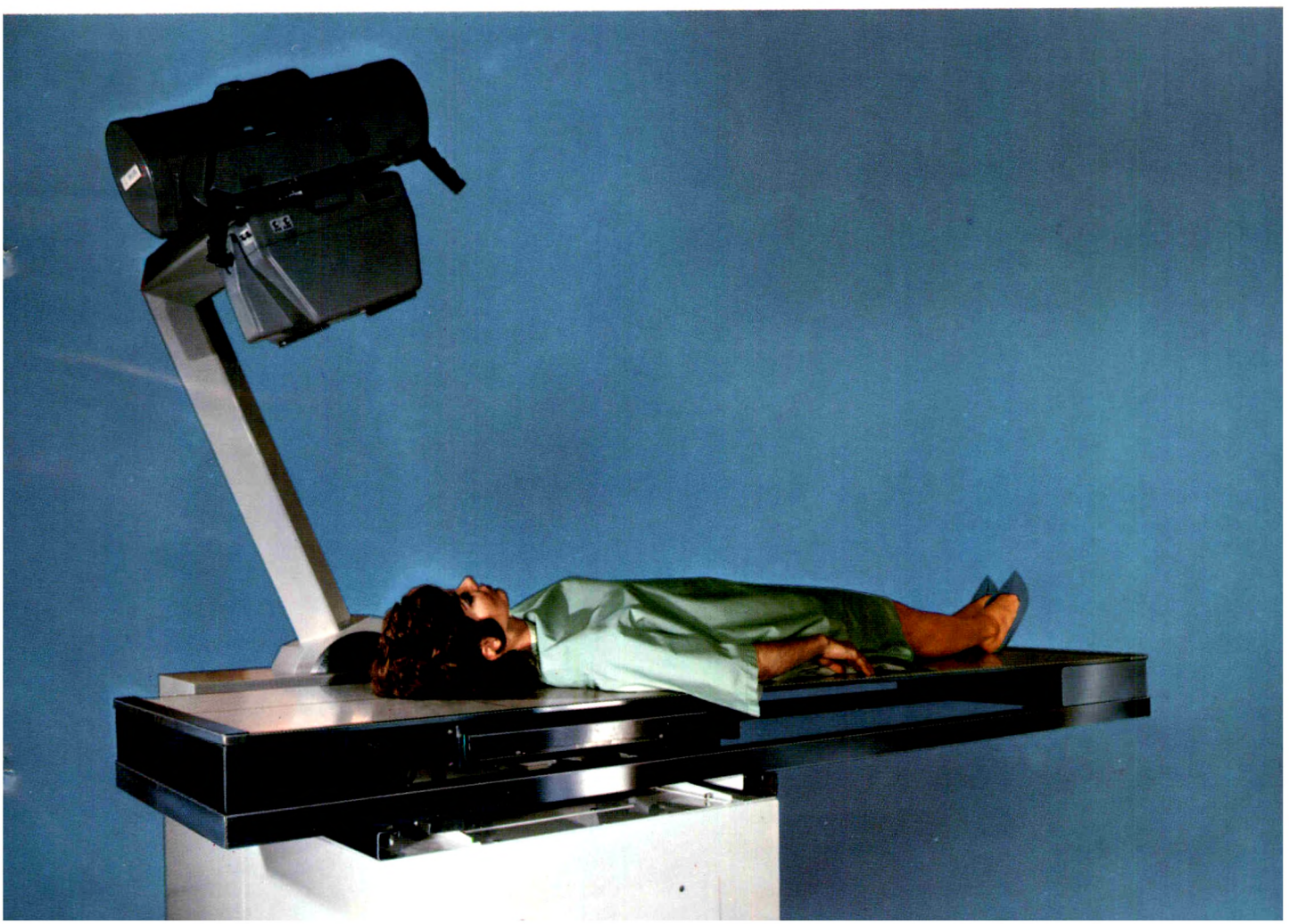

BOOKS FOR THE CARDIOLOGIST

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Bellet—Clinical Disorders of the Heart Beat

By the late SAMUEL BELLET, M.D., School of Medicine, University of Pennsylvania. x plus 1317 pages, 7″ x 10″. 1150 illustrations on 470 figures. 6 plates in color. 120 charts. 32 tables. *New (3rd) edition. 1971.* $52.50. (ISBN: 0-8121-0307-6).

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Conn and Horwitz—Cardiac and Vascular Diseases

Edited by HADLEY L. CONN, JR., M.D., and ORVILLE HORWITZ, M.D., School of Medicine, University of Pennsylvania. 102 CONTRIBUTORS. Two volumes totaling 1878 pages, 7″ x 10″. 605 figures. Complete index in both volumes. *1971.* $39.50. (ISBN: 0-8121-0043-3).

A Broad-Scope, Practical Presentation

This book presents a rational basis for the relation of basic sciences to clinical cardiology. Diseases affecting the heart and blood vessels (great and small) and ramifications of these diseases are discussed thoroughly. Diseases of other organs and their effects on the heart and blood vessels are given proportionable coverage. No other work so effectively bridges the gap between laboratory findings and their clinical applications. It truly reflects the essence of the "compleat" cardiologist. The list of contributors to this two-volume work boasts some of the nation's outstanding cardiologists and distinguished teachers in many medical disciplines. "This book underscores an immensely important concept. The editors are to be commended." —*The American Journal of Cardiology.*

Yu & Goodwin—Progress in Cardiology

By PAUL N. YU, M.D., University of Rochester (N.Y.) Medical Center; and JOHN F. GOODWIN, M.D., Royal Postgraduate Medical School, London, England. xii plus 283 pages, 7″ x 10″. 123 illustrations. *New. 1972.* $15.00. (ISBN: 0-8121-0326-2).

A comprehensive review of the status of ten of the most important problems in cardiology. Includes computers in cardiology as they relate to data collection, analysis, display and retrieval; genesis, diagnosis and management of cardiac arrhythmias in acute myocardial infarction; interaction of cardiac drugs; direct and indirect techniques of measured performance of the heart; control of peripheral veins; surgical treatment of coronary artery diseases, etc.

Winsor—Primer of Vectorcardiography

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This monograph will assist the clinician in solving some of his difficult problems by helping him to read vectorcardiograms quantitatively and accurately. It is intended for use by cardiologists and fills the need for a practical text to assist the clinician with vectorcardiographic interpretations. A new computerized method of calculating the spatial vectorcardiogram in numerical form adds to the diagnostic value of conventional planar vectorcardiography.

Burch and Winsor—A Primer of Electrocardiography

By GEORGE E. BURCH, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, New Orleans; and TRAVIS WINSOR, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Director of the Wiley Winsor Memorial Heart Research Foundation, Los Angeles. xiv plus 292 pages. 287 illustrations. *New (6th) edition. 1972.* $7.75. (ISBN: 0-8121-0337-8).

Crystallized in this clearly written primer are the facts necessary for all who are starting to learn about, understand and interpret electrocardiograms. The theoretic and many practical aspects of electrocardiography are covered fully and presented from a mechanistic viewpoint.

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*Recommendations for Standardization of leads and of specifications for Instruments in Electrocardiography and Vector Cardiography from Report of Committee on Electrocardiography, American Heart Association, Circulation, Volume XXXV, March 1967.

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He wakes up alert and ready to face the demands of the day (Quāālude patients usually awaken easily and without evidence of "hangover")... because he slept well all night (Quāālude usually helps produce 6 to 8 hours of restful sleep)... and he didn't have to lie awake for a long period of time before he went to sleep (Quāālude can induce sleep in 10 to 30 minutes). Now the physician has one less tired, sleepy and apprehensive patient to contend with.

Non-barbiturate Quāālude-300 is chemically unrelated to other sedative-hypnotics. Its therapeutic value has been established in controlled clinical studies and by wide usage of methaqualone throughout the world.

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For these reasons, maybe the prescribing physician sleeps a little better, too.

a non-barbiturate

Quāālude®-300
(methaqualone) 300 mg. tablets

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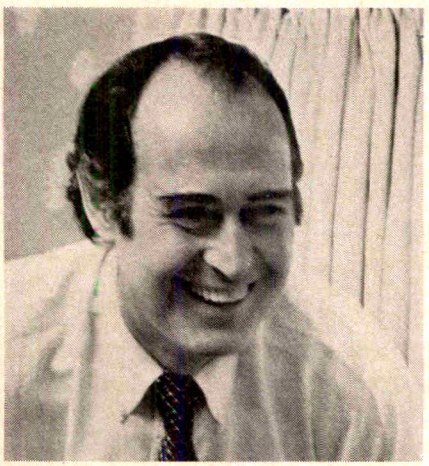
For additional prescribing information, please turn page.

A good morning after a sleep-through night



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sleep duration—6-8 hours
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Brief Summary
of Prescribing Information

Indications:
Sleep. Daytime sedation.

Usual Adult Dose:
For sleep, 150-300 mg. at bedtime. For patients previously on other hypnotics, 300 mg. for five to seven nights. *For sedation,* 75 mg. t.i.d. or q.i.d. Not recommended in children. Dosage should be individualized for aged, debilitated or highly agitated patients.

Overdosage:
Acute overdosage may result in delirium and coma, with restlessness and hypertonia, progressing to convulsions. Evacuate gastric contents, maintain adequate ventilation and support blood pressure, if necessary. Dialysis may be helpful. Analeptics are contraindicated. Succinylcholine accompanied by assisted respiration has been proposed for prolonged convulsions. Overdoses of methaqualone appear to be less often associated with cardiac or respiratory depression than are overdoses of oral barbiturates, but shock and respiratory arrest may occasionally occur.

Contraindications:
Contraindicated in women who are or may become pregnant; or patients with known hypersensitivity.

Warnings:
Take hypnotic dose only at bedtime. Not recommended in children. Warn patient on Quāālude against driving a car or operating dangerous machinery. Care needed when administered with other sedative, analgesic or psychotropic drugs or alcohol because of possible additive effects. Pending longer clinical experience, Quāālude should not be used continuously for periods exceeding three months. *Psychological dependence* occasionally occurs. *Physical dependence* rarely reported. However, caution needed with addiction-prone patients.

Precautions:
Use with caution and prescribe small quantities in patients with anxiety states where impending depression or suicidal tendencies exist. Give in reduced doses, if at all, in patients with impaired hepatic function.

Adverse Reactions:
Neuropsychiatric: headache, hangover, fatigue, dizziness, torpor, transient paresthesia of the extremities. An occasional patient has experienced restlessness or anxiety. *Hematologic:* aplastic anemia possibly related to methaqualone has been very rarely reported. *Gastrointestinal:* dry mouth, anorexia, nausea, emesis, epigastric discomfort, diarrhea. *Dermatologic:* diaphoresis, bromhidrosis, exanthema. Urticaria has been particularly well documented.

Supplied:
Quāālude-150 (150 mg. white, scored tablets). Quāālude-300 (300 mg. white, scored tablets).

Consult complete literature before prescribing.

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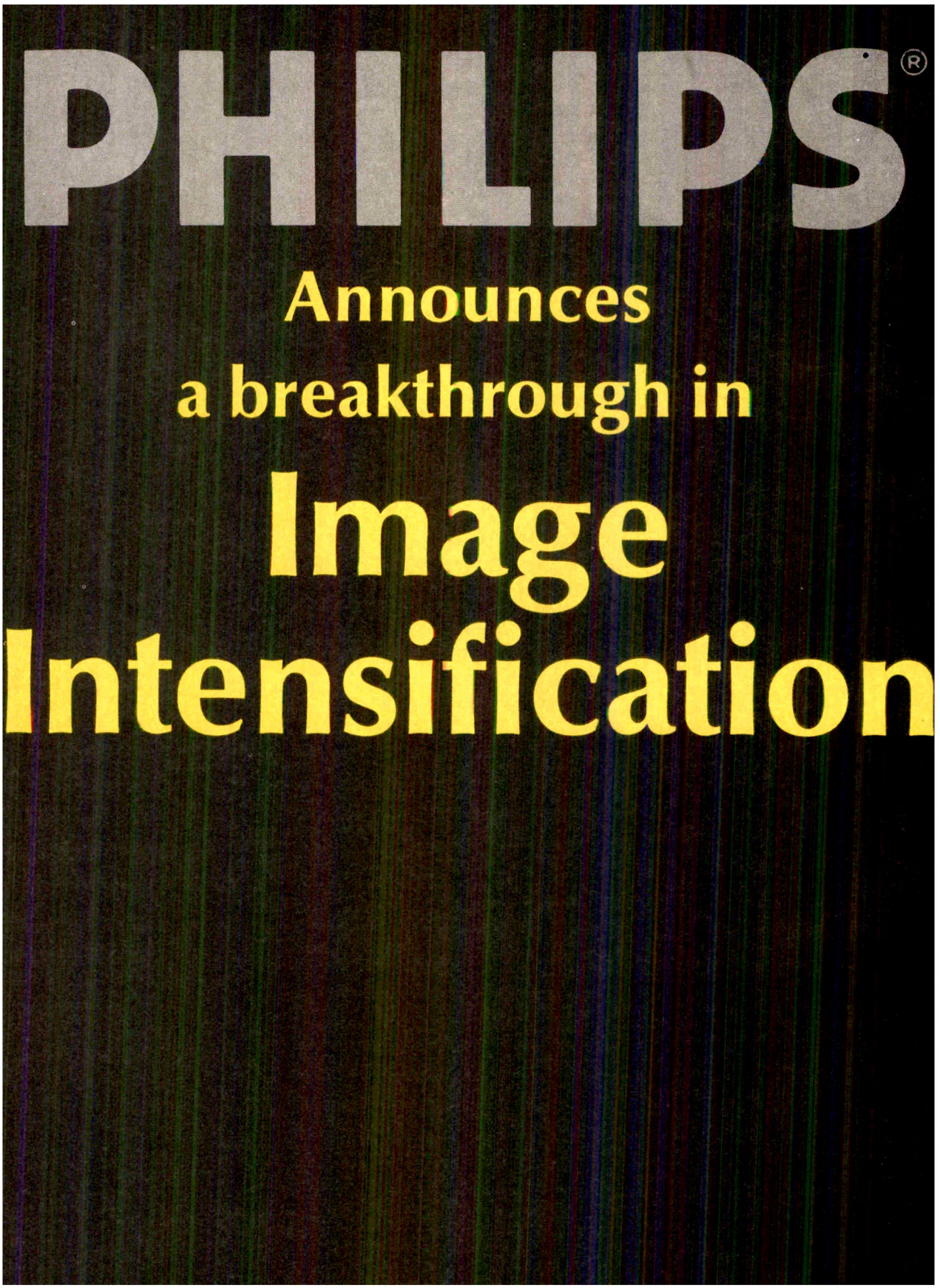
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The good-tasting way to treat hypokalemias induced by thiazide diuretics and other drugs...

Here, at last, is a potassium chloride supplement that just doesn't taste like one! The mixed fruit flavor of new K-Lyte/Cl is truly refreshing. Now, K-Lyte/Cl offers your patients all of the therapeutic advantages you expect from a potassium chloride supplement. And you can be sure that your patients will take the K-Lyte/Cl you prescribe—all in good taste.

Now you have a choice...

When extra chloride is not desired, original effervescent K-Lyte is unsurpassed in flavor, effective and safe in short- or long-term potassium supplementation. There is little chance of taste fatigue from K-Lyte with two delicious, effervescent flavors to alternate...fresh-tasting orange and sparkling lime.

K-Lyte® Each effervescent tablet in solution supplies 25 mEq. potassium as bicarbonate and citrate

K-Lyte®/Cl Each dose of powder in solution supplies 25 mEq. potassium chloride

Each tablet or dose must be completely dissolved before taking.

Indications: K-Lyte and K-Lyte/Cl are oral potassium supplements for therapy or prophylaxis of potassium deficiency. Particularly useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses. **Contraindications:** Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause. **Warnings and Precautions:** Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water. K-Lyte/Cl contains 4.9 grams (20 calories) of sucrose per dose which should be considered for patients with restriction of caloric intake. **Adverse Reactions:** Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts. **Dosage and Administration:** Adults: 1 tablet or dose *completely dissolved*, 2 to 4 times daily, depending upon the requirements of the patient: K-Lyte: 1 tablet (25 mEq. potassium) in *3 to 4 ounces of cold or ice water;* K-Lyte/Cl: 1 dose (25 mEq. potassium chloride) in *6 ounces of cold or ice water.* The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: *It is suggested that these products be taken with meals and sipped slowly over a 5-10 minute period.* **How Supplied:** K-Lyte: Effervescent tablets—boxes of 30 and 250 (orange or lime flavors). K-Lyte/Cl: Powder, cans of 30 measured doses with scoop (fruit-punch flavor). ℞

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Albert N. Brest, MD, Editor-in-Chief

Volume 3 is now complete!

With the publication of Cardiac Surgery II (Volume 3, Number 3) another outstanding volume of Cardiovascular Clinics becomes available. The distinguished guest editor of this number (and Number 2, Cardiac Surgery I) is Dwight E. Harken. In his preface to Surgery I, Dr. Paul Dudley White describes Dr. Harken as *'one of the most important cardiac surgical pioneers of all the history of cardiac surgery.'*

These two issues on cardiac surgery offer a broad base of information which has been carefully assembled to be of real help to the clinician. They explore in great detail virtually all of the important clinical aspects of cardiac surgery . . . indications for surgery, technical considerations, pre- and post-operative care, anesthesia, cardiopulmonary bypass, assisted circulation, prosthetic and biologic valves, pacemakers, cardiac transplantation. This material will be of immense value to the physician who must make a recommendation regarding surgery and who must, also, manage his patient after the operation.

Vol 3, No 3, Cardiac Surgery II. (Dwight E. Harken, MD, Guest Editor) 200 pages, illustrated.

Vol 3, No 2, Cardiac Surgery I (Dwight E. Harken, MD, Guest Editor) 330 pages, 85 illustrations.

Vol 3, No 1, Peripheral Vascular Disease (Ray W. Gifford, Jr., MD, Guest Editor) 290 pages, 93 illustrations.

VOLUME 3 (3 numbers) $27.50.
Individual numbers, $12.

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In his foreword, Dr. John W. Kirklin, of the Department of Surgery at the University of Alabama says: 'This book . . . is an exemplary monograph. In simple terms, Mr. Braimbridge details the important aspects of the care of seriously ill patients . . . This work is recommended for serious study by medical students, house officers, nurses, paramedical persons, and indeed by experienced surgeons. Each group will get something different from the monograph, but each will get something enormously worthwhile.'

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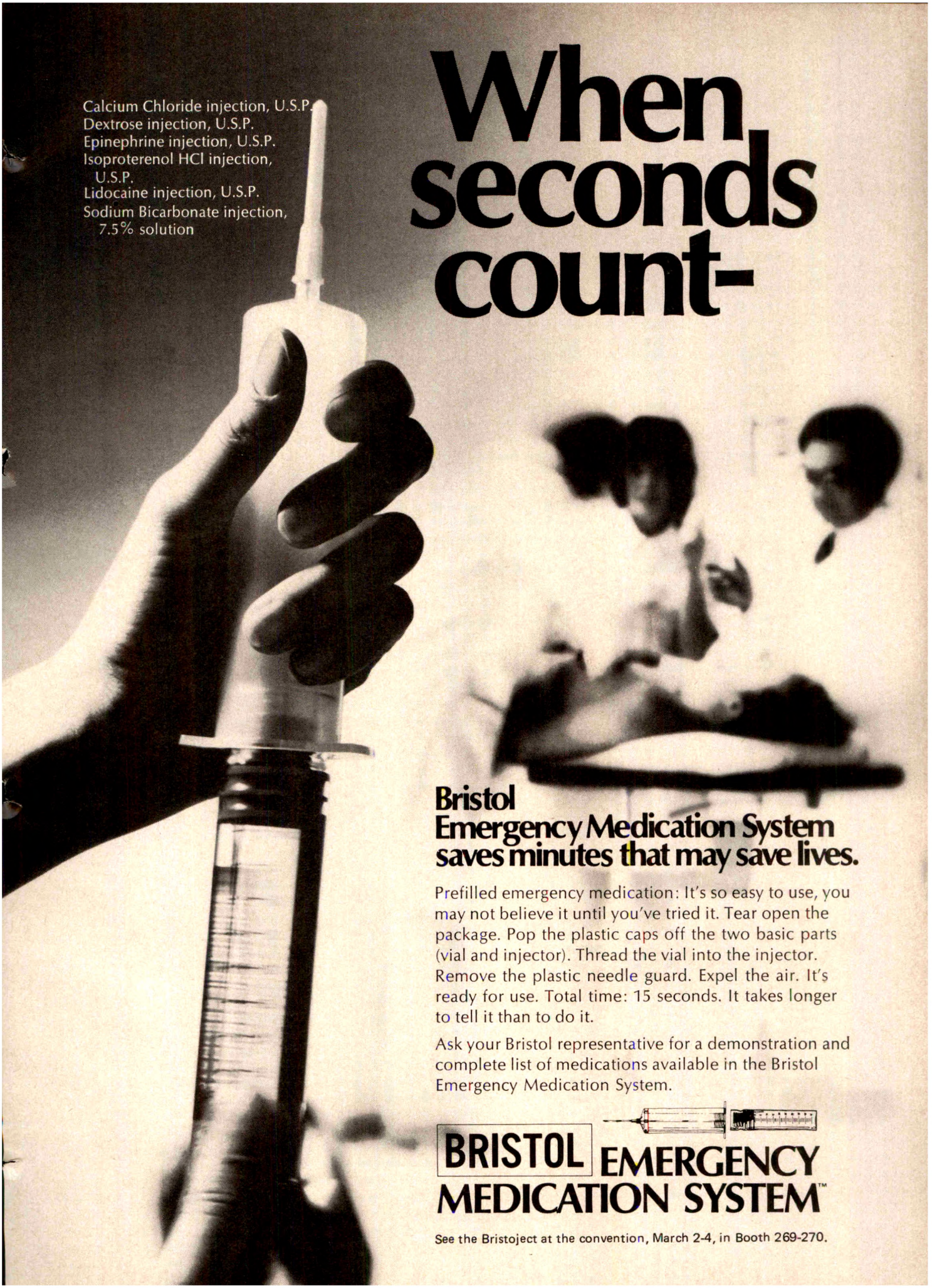

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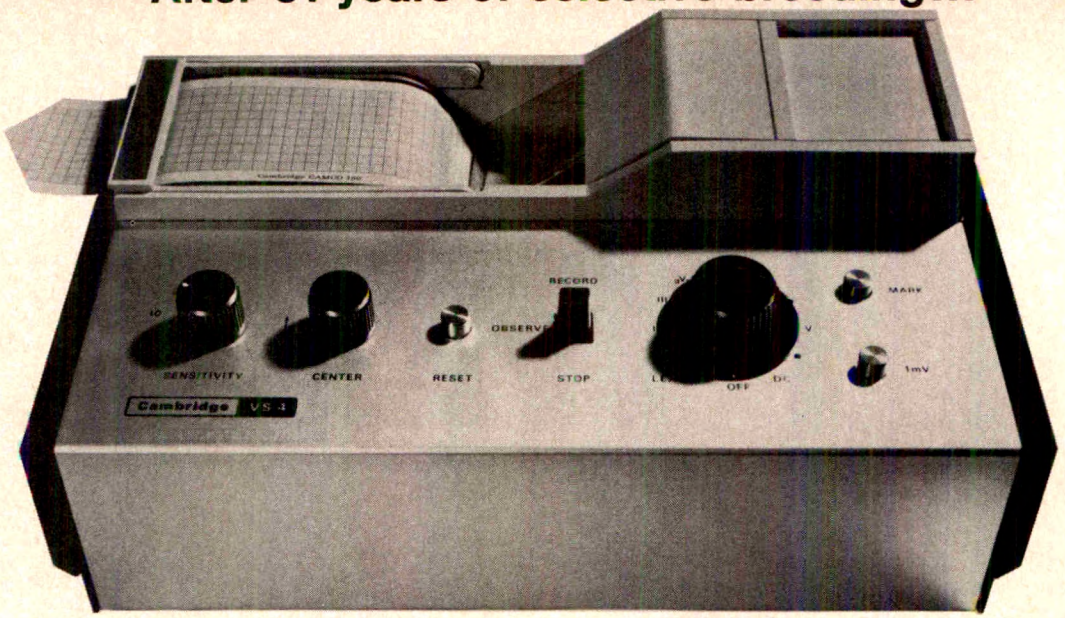

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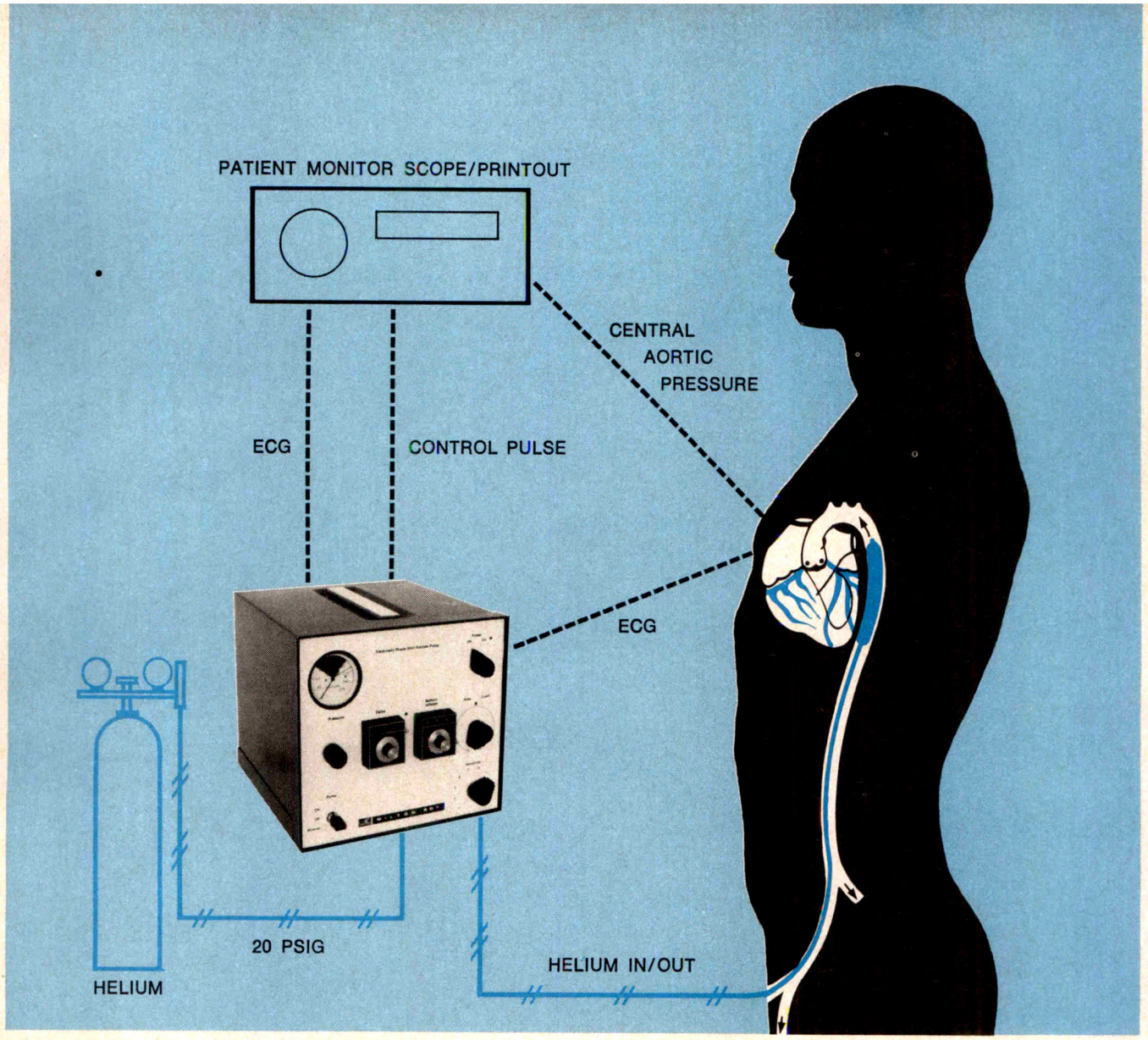

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The Kantrowitz System and the procedure associated with its use are described in an 8-page brochure, which can be obtained from Milton Roy Company, P. O. Box 12169, St. Petersburg, Florida 33733. Telephone (813) 544-2581.

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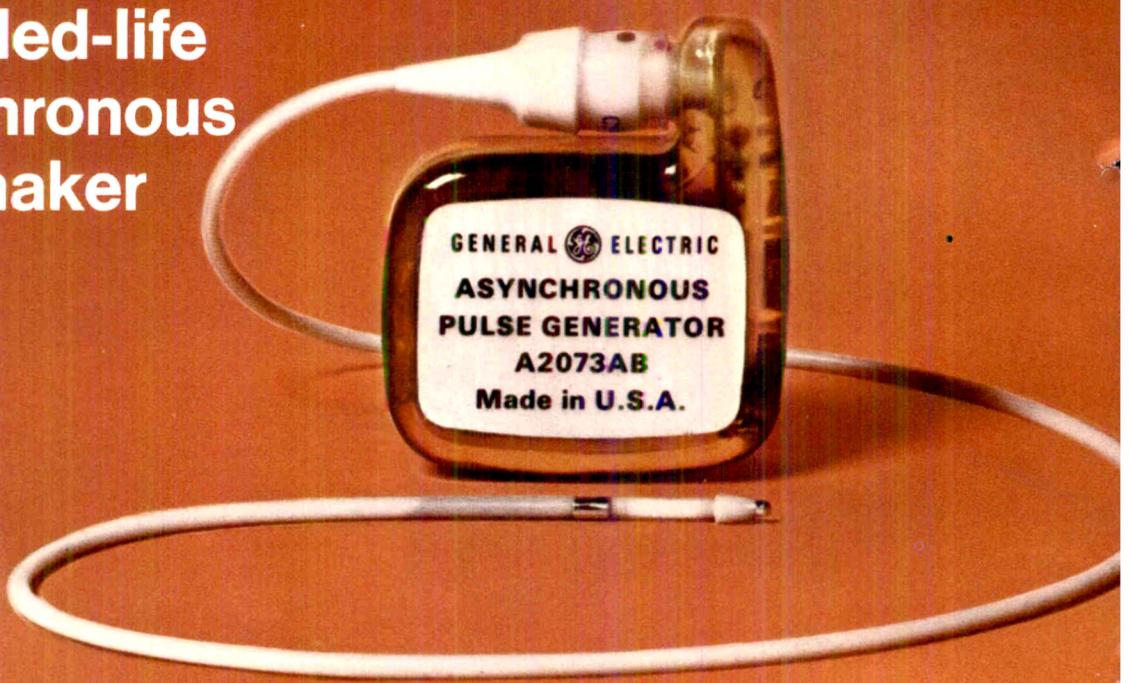

The asynchronous that gives you the choice.

Into this single, more compact unit, General Electric has incorporated features no other pacemaker has. Features that give longer unit life, plus new power and pacing redundancy for greater patient safety. And the implanting physician now has important options he's never had before.

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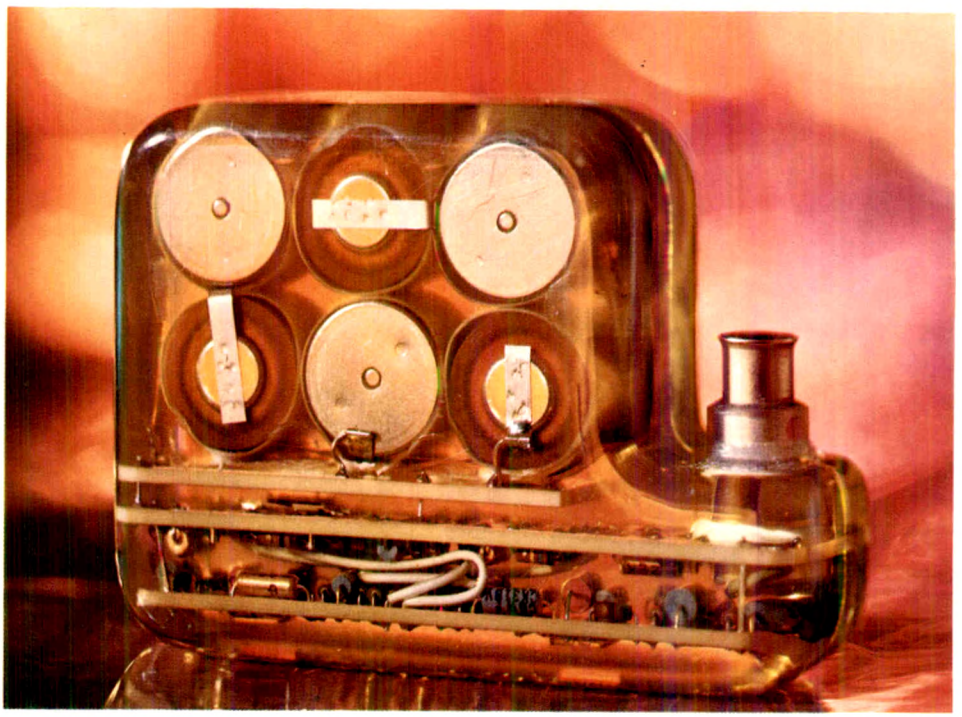
General Electric has set the pace in pacemaker technology:



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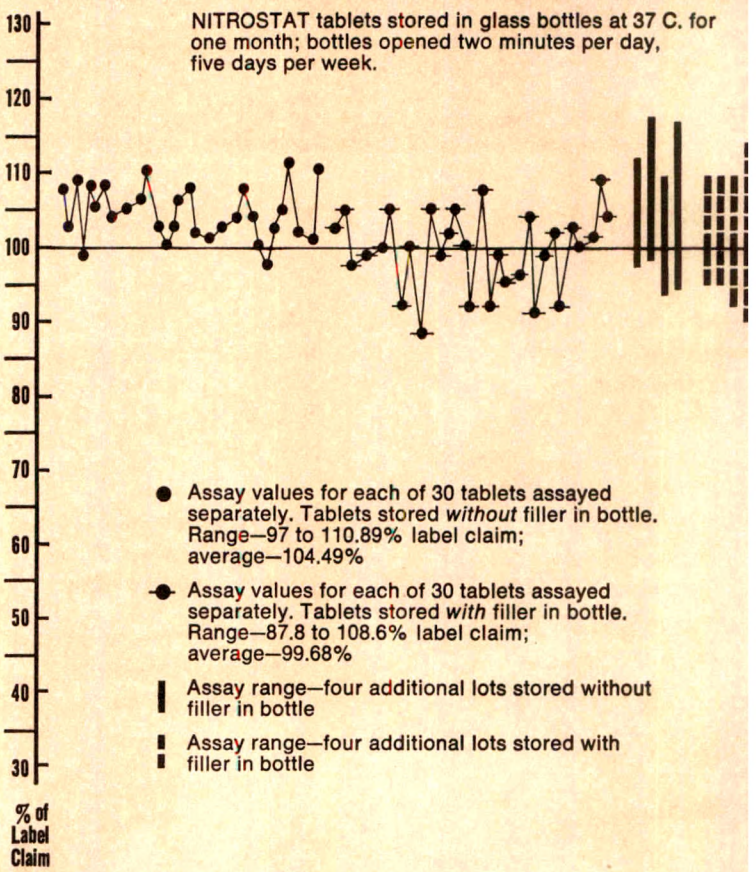

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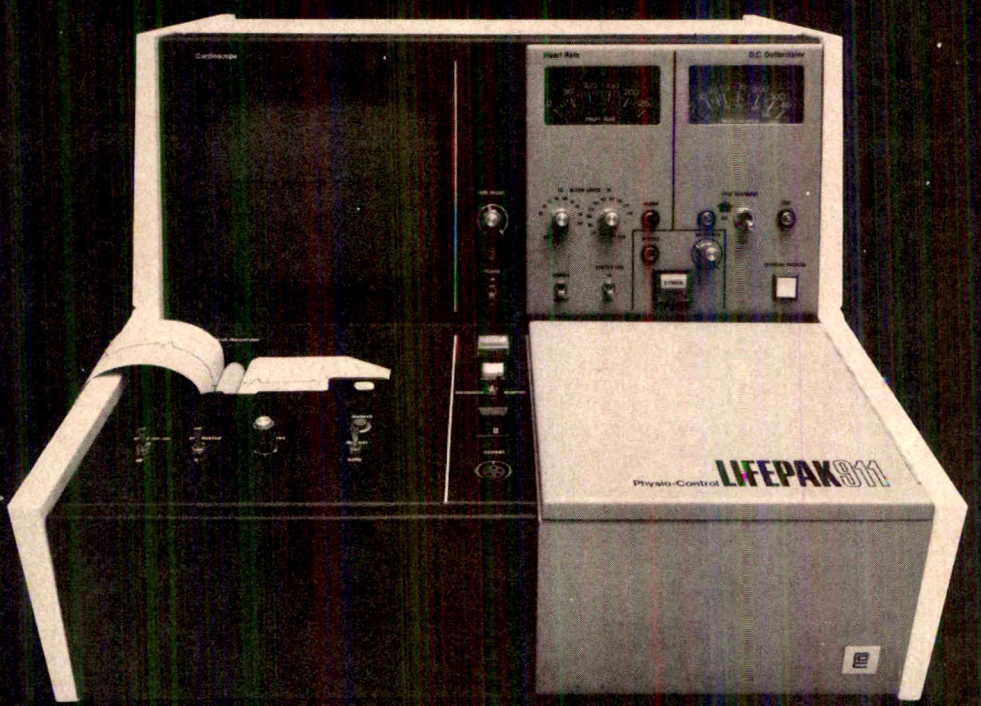

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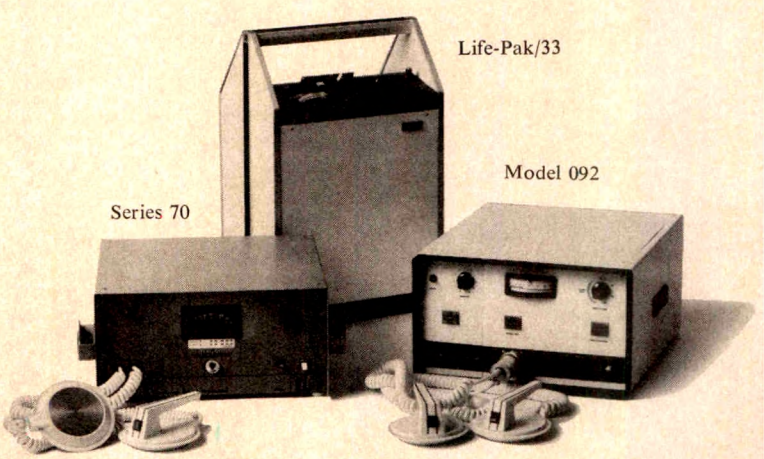

A specific thyroid analogue is available for the treatment of

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INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. STRICT ATTENTION SHOULD BE PAID TO THE INDICATIONS AND CONTRAINDICATIONS. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS IN EUTHYROID PATIENTS: 1) Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status. 2) Hypertensive states (other than mild, labile systolic hypertension). 3) Advanced liver or kidney disease. 4) Pregnancy. 5) Nursing mothers. 6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; when either or both are present, the advantages of sodium dextrothyroxine therapy must be weighed against the possibility of deleterious results.

WARNINGS: BECAUSE THE EFFECTS OF ANTICOAGULANTS MAY BE POTENTIATED, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY AND READJUST AS NECESSARY ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. CONCENTRATION OF FACTORS VII, VIII, IX, AND PLATELET ACTIVITY SHOULD ALSO BE MONITORED, SINCE THESE FACTORS MAY BE DECREASED. CONSIDER WITHDRAWAL OF CHOLOXIN 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients with cardiac disease is required, and the drug should be withdrawn or dosage reduced if aggravation of angina, increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops. Hypothyroid patients are more sensitive than euthyroid patients, especially if treated concomitantly with other thyroid preparations. Special consideration must be given to the dosage of the hypothyroid patient.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias or coronary insufficiency. Drug withdrawal or careful observation of patients receiving such injections is recommended, especially before elective surgery. In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and subsequent readjustment if dextrothyroxine is later withdrawn.

USAGE IN WOMEN OF CHILDBEARING AGE: Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of Choloxin to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

PRECAUTIONS: Unusually high PBI values are common in treated patients and are not evidence of hypermetabolism. In children, use only when a significant cholesterol-lowering effect is observed. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism and thus more common in the hypothyroid patient, especially the hypothyroid cardiac. Cardiac changes have rarely been precipitated in non-cardiac patients: Angina pectoris (0.2% incidence), arrhythmia (0.5%), myocardial ischemia (<0.1%), cardiomegaly (<0.1%), fatal and non-fatal myocardial infarctions (<0.2%): Insomnia, nervousness, palpitations, tremors, weight loss, lid lag, sweating, flushing, hyperthermia, hair loss, changes in bowel habits, diuresis, and menstrual irregularities may also be related to the metabolic action. A few patients developed itching and skin rashes, apparently from iodism.

Dyspepsia, nausea and vomiting, and changes in appetite occurred in less than 1%. Headache, changes in libido, hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain and bizarre complaints were reported in less than 1% of treated patients. Gallstones were newly discovered in 13 patients, and cholestatic jaundice in one, although relationship to drug therapy was not established. In a total of 19 patients, pre-existing peripheral vascular disease, exophthalmos, retinopathy, and disturbed sensorium continued to worsen. Cerebrovascular accidents, thrombophlebitis, and G.I. hemorrhages each occurred in less than 1% of patients, but there appears to be no relationship to dextrothyroxine therapy.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

DOSAGE RECOMMENDATIONS: For *adult* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is 4.0 to 8.0 mg. per day. The initial daily dose should be 1.0 to 2.0 mg. to be increased in 1.0 or 2.0 mg. increments at intervals of not less than one month to a maximum level of 6.0 to 8.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol. When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients, the more conservative dosage schedule is recommended.

For *pediatric* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is approximately 0.1 mg./kg. The initial daily dosage should be approximately 0.05 mg./kg., to be increased in 0.05 mg./kg. increments at monthly intervals. The recommended maximal dose is 4.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

HOW SUPPLIED: Choloxin brand of sodium dextrothyroxine is supplied in prescription packages of 30 and 100 scored, 2 mg. (yellow) and 4 mg. (white) tablets.

An Important Note: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

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Our intra-aortic balloon* is unique. The Dual-Chamber Intra-Aortic Balloon. It pumps blood preferentially towards the heart during balloon inflation. Experimental data[1] show an average increase of 66-100% in coronary blood flow over and above that obtained with a single-chamber balloon.

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1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

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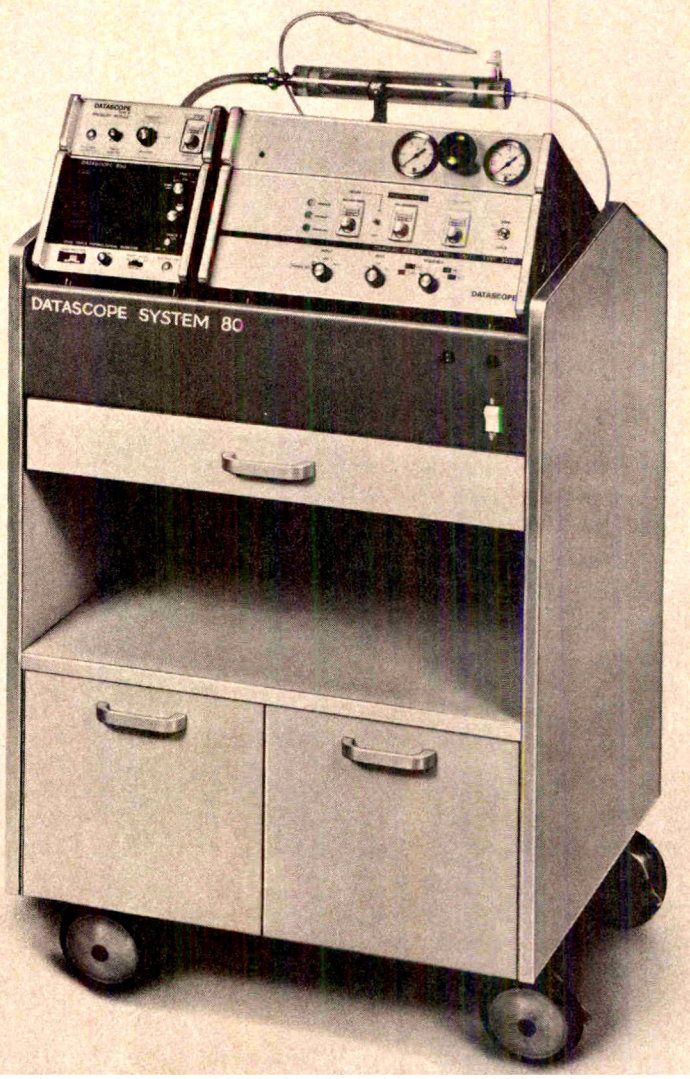

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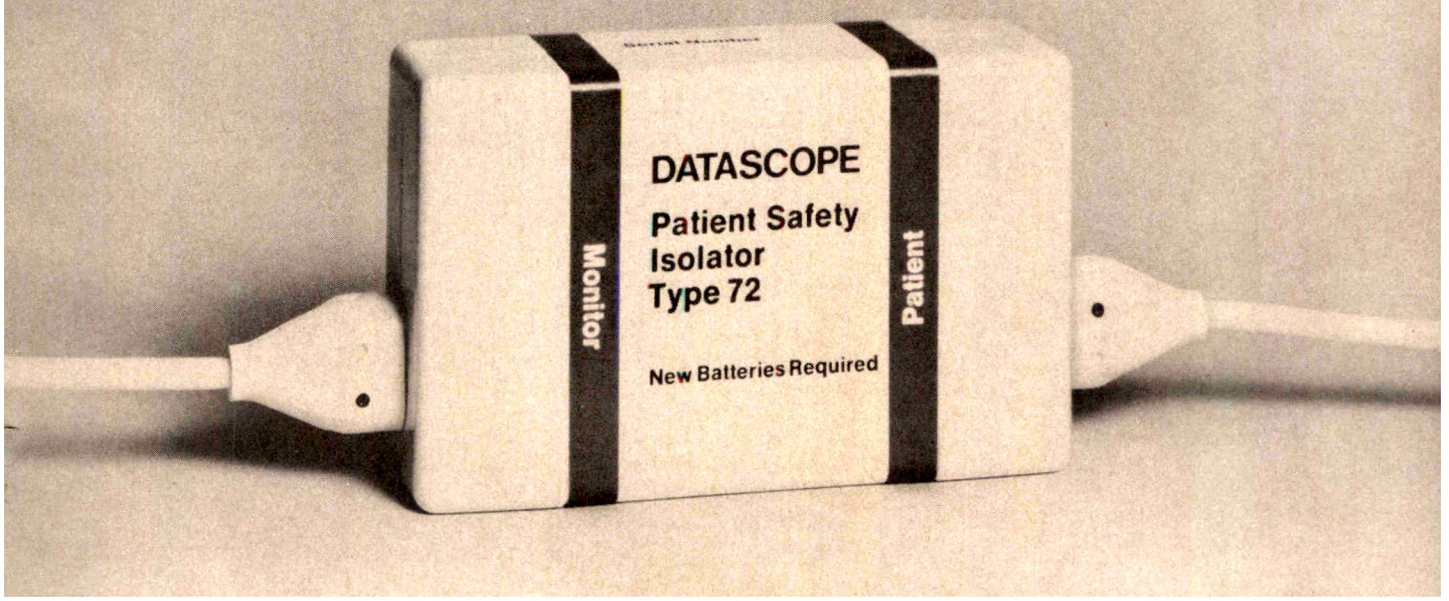

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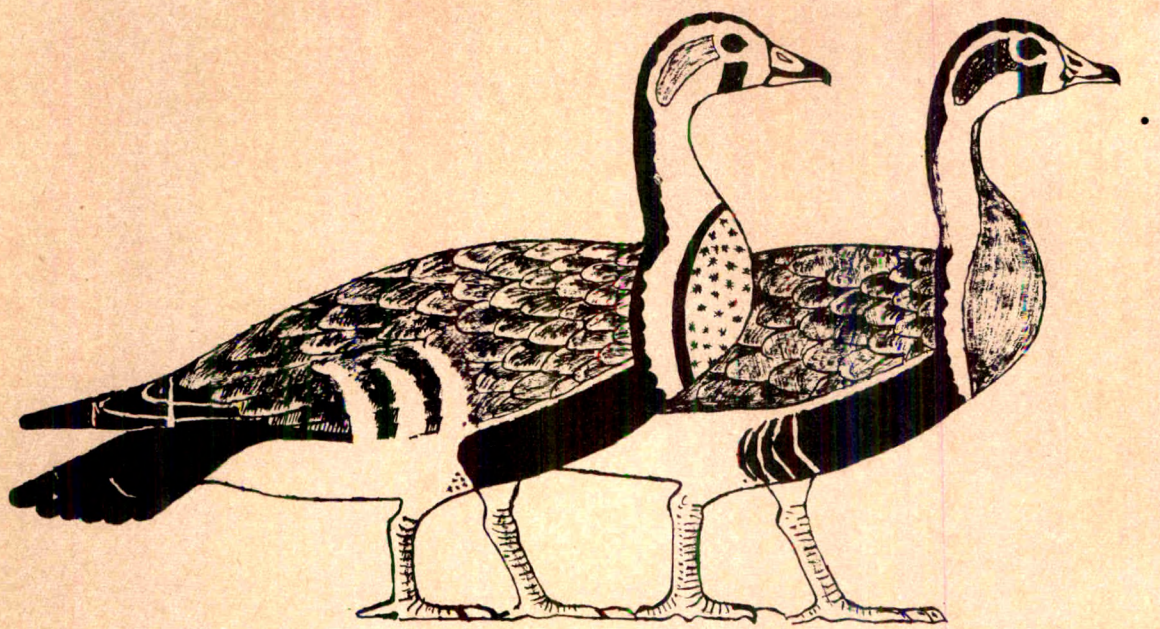

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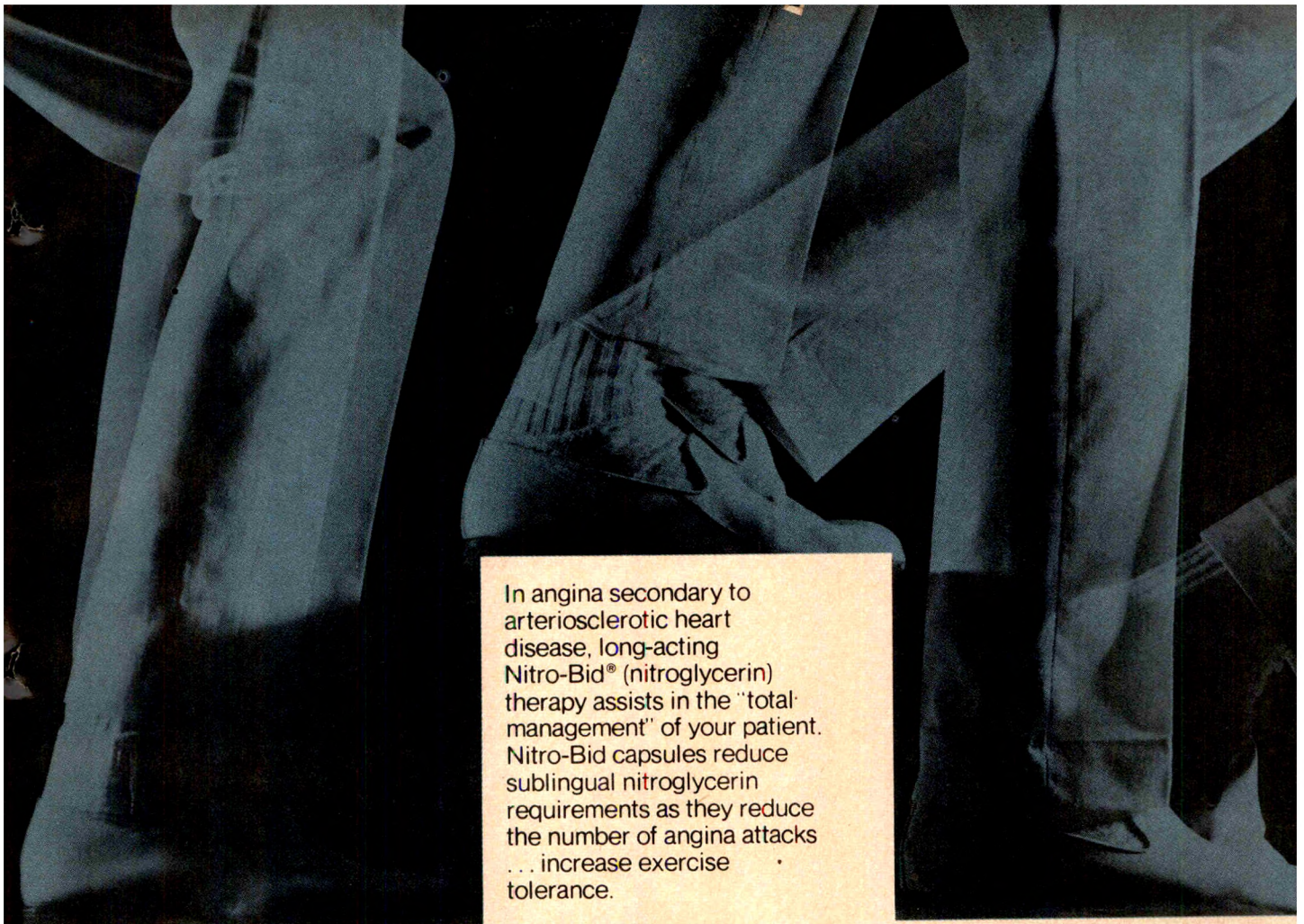

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Dosage: One capsule two or three times daily at 8 to 12 hour intervals.

Reference:

1. Master, A. M.: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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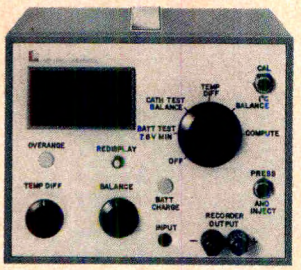

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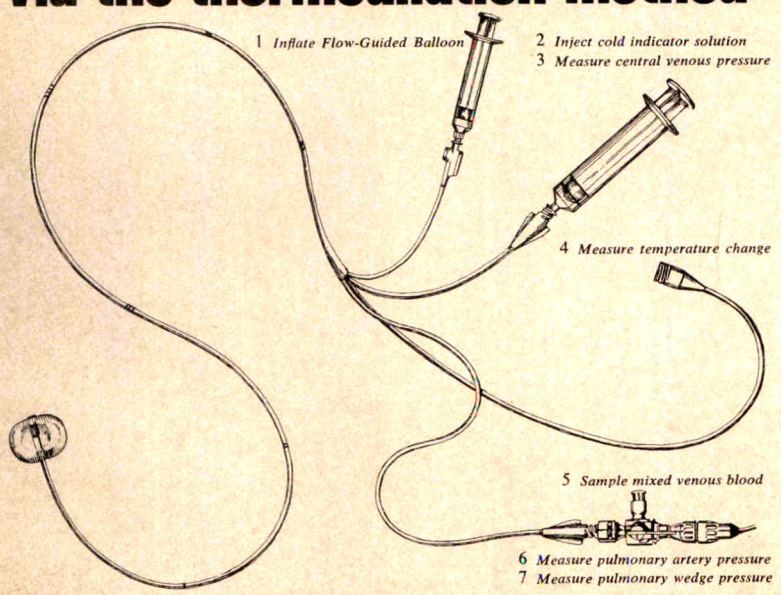

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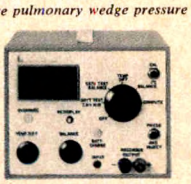

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Consult direction circular before prescribing.

1. Edelman, B.A., Contractor, A.M., and Shangraw, R.F.: The stability of hypodermic tablets of nitroglycerin packaged in dispensing containers, J. Amer. Pharm. Ass. NS11:30 (January) 1971.

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FEBRUARY, 1972

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VOLUME 29

NUMBER 2

Clinical Studies

Clinical Response to Nitroglycerin as a Diagnostic Test for Coronary Artery Disease

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Boston, Massachusetts

The clinical response to nitroglycerin was correlated with the results of coronary angiography in 70 patients with chest pain of the anginal type: 49 patients with coronary artery disease and 21 without demonstrable cardiac disease. Of the patients with coronary disease, 76 percent were regularly relieved of pain in 3 minutes or less; 16 percent required more than 3 minutes for relief; and 8 percent were not relieved by the drug. Of the patients without coronary disease, only 19 percent consistently obtained relief in 3 minutes or less. Patients with coronary disease whose response to nitroglycerin was delayed or absent tended to have more frequent and intense pain, more coronary arteries involved by obstructive lesions and more hemodynamic or wall motion abnormalities than those who had prompt relief. Severe or bizarre side effects were common in patients without coronary disease but rare in patients with disease. It is concluded that 90 percent of patients with recurrent, angina-like chest pain who exhibit a prompt response to nitroglycerin have coronary artery disease; a delayed or absent response paradoxically indicates either absence of coronary artery disease or unusually severe disease and angina.

From the Cardiovascular Division, Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass. This study was supported by U. S. Public Health Service Grants PO-1 HE-11306 and IT 1 HE-5679, and the Women's Aid for Heart Research, Boston, Mass. Manuscript received January 18, 1971, accepted March 25, 1971.

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It has been known since 1879 that nitroglycerin alleviates angina pectoris.[1] Because of its therapeutic efficacy in this condition, the clinical response to the drug is frequently utilized as a diagnostic test to differentiate pain due to coronary artery disease from pain of other origin. However, definition of the positive response to nitroglycerin has been formulated by clinicians whose careful observations of the drug's effects were usually made without objective evidence of the presence of significant coronary artery disease in their patients.[1–4]

The recent advent of coronary angiography[5,6] has permitted the accurate diagnosis of coronary artery disease during life. Application of this technique has uncovered a group of patients with a pain pattern compatible with angina pectoris but no visible obstructive coronary artery lesions on angiograms.[7] Identifica-

TABLE I

Questions for Assessment of Clinical Response to Nitroglycerin

1. How long have you been using nitroglycerin?
2. How often is nitroglycerin taken?
3. Dosage?
4. Does nitroglycerin relieve pain? All types of pain? Is relief complete or incomplete?
5. How long after nitroglycerin is taken is pain relieved?
6. Is there a difference in effect of nitroglycerin taken near onset of pain rather than after several minutes?
7. Do you presently, or have you ever, experienced headaches with nitroglycerin? If so, describe headaches.
8. Have you ever experienced dizziness or faintness or any other unusual sensations after nitroglycerin?
9. Did propranolol or long-acting nitrate or nitrite preparations affect response to nitroglycerin?

tion of this group raises the question of whether previous reports of the effects of nitroglycerin in angina were sufficiently accurate, inasmuch as some of the patients observed may not have had coronary artery disease, whereas others, with atypical symptoms, may have had unrecognized coronary disease.

This study was designed to assess the value of the subjective response to nitroglycerin, reported in a standardized interview, as an aid to diagnosing obstructive coronary artery disease. Response to the drug was correlated with the results of coronary angiography in 70 patients with chest pain of the anginal type. The population comprised 49 patients with coronary artery disease and 21 patients without demonstrable coronary lesions.

Methods

The 70 subjects were admitted to the Peter Bent Brigham Hospital for cardiac catheterization and coronary angiography. All had been diagnosed by their referring physician as having probable or possible coronary artery disease with angina pectoris, and all had used nitroglycerin. There were 18 women and 52 men ranging in age from 30 to 68 years. The duration of symptoms ranged from 2 months to 14 years.

Each patient was carefully questioned about his experience with nitroglycerin. A printed form was completed by the questioner (one of us) to assure uniform and complete gathering of information (Table I). In 75 percent of cases neither the questioner nor the patient knew the results of the cardiac catheterization at the time of the interview. The frequency and duration of usage of nitroglycerin and its effectiveness in relieving the patient's chest pain were ascertained. The temporal relations among onset of pain, ingestion of nitroglycerin and relief of pain were elicited. The incidence of headache, dizziness, syncope and other side effects of the drug was noted. Inquiries were made as to whether nitrite, nitrate preparations or propranolol influenced response to nitroglycerin. In all patients who reported a delayed or absent response, a careful inquiry was made concerning: freshness of tablets and adequacy of dosage. No patient had used tablets more than 1 year old; almost all patients used 0.3 or 0.4 mg tablets, and virtually all had tried more than 1 tablet at a time in search of relief.

Selective coronary angiography by either the Sones'[5] or Judkins[6] technique was performed on all subjects. A General Electric or Siemens image intensifier system and 16 mm film were used. Multiple projections of each artery were obtained. The films were reviewed by several observers and were judged in each instance to be of adequate quality for accurate morphologic diagnosis. Disease in a coronary artery was considered significant if there was total occlusion or stenosis constricting the lumen by more than 75 percent. Vessels were described in terms of 1, 2 or 3 vessel involvement, referring to the 3 major coronary arterial systems: left anterior descending, left circumflex and right coronary arteries. The presence or absence of collateral channels filling diseased vessels was carefully noted by (1) direct visualization of accessory blood vessels either filling the distal segment of an occluded or severely stenotic artery, or subserving the area of myocardium that would ordinarily be supplied by the severely stenotic artery; and (2) visualization of a coronary artery after injection of contrast material into the contralateral vessel.

Right- and left-sided cardiac pressures were measured with Statham P23Db transducers. Cardiac output was obtained with the dye-dilution technique, utilizing indocyanine green dye as the indicator. Cineventriculography was performed in all subjects by power injection of 30 to 40 ml of 75 percent sodium and meglumine diatrizoate into the left ventricle through a multiple hole catheter, with the patient in the right anterior oblique position. Approximately 20 percent of the ventriculograms were biplane, the remainder single plane. Any abnormal patterns of contraction were noted, such as diminished or absent motion of a portion of the wall, paradoxical systolic motion of a portion of the wall or a disturbed temporal sequence of contraction.[8] Significant hemodynamic abnormalities encountered consisted of increased left (>12 mm Hg) or right (>6 mm Hg) ventricular end-diastolic pressure or a low cardiac index (<2.5 liters/min per m^2). No patients with significant cardiac valvular lesions were included in the study.

Results

Forty-nine patients, 42 male and 7 female, had obstructive coronary artery disease, and 21 patients, 10 male and 11 female, had either morphologically normal vessels or insignificant stenosis of their vessels (<25 percent). Six patients without coronary artery disease had other demonstrable possible causes for pain: 3 had chronic cholecystitis with cholelithiasis, 1 had probable post-thoracotomy syndrome, 1 had a fractured cervical vertebra, and 1 had severe cervical arthritis. None of the patients with normal vessels had hemodynamic or wall motion abnormalities.

Effect of nitroglycerin in patients with coronary disease: Thirty-seven of the 49 patients with coronary artery disease (76 percent) reported that

their pain was usually or always relieved in less than 3 minutes after sublingual administration of nitroglycerin (Table II). In these patients with rapid response, pain was almost always completely relieved without residual discomfort; 18 reported consistent relief in less than a minute. The group with rapid response included all patients with only 1 vessel involvement (Table III). Hemodynamic and wall motion abnormalities were less common than in patients with delayed or absent responses to the drug (Table III).

Eight patients with coronary artery disease (16 percent) regularly experienced relief of pain with nitroglycerin only after an interval of 3 or more minutes. The interval was usually approximately 5 but ranged from 4 to 15 minutes. All 8 patients claimed that relief with nitroglycerin was more rapid and complete than would have occurred spontaneously without the drug. Two of these patients had previously been accustomed to rapid relief but after several years of nitroglycerin therapy for angina had noted that the drug took longer to act. Patients with delayed response characteristically had unusually frequent (typically several times a day), unusually intense anginal pain, which tended to be precipitated by relatively mild exertion and often occurred nocturnally, postprandially or at rest. Relief of pain in this group was often incomplete; a dull ache or other residual discomfort was common, although the intensity of the pain was noticeably diminished. These patients also tended to have more widespread and severe disease at cardiac catheterization than patients who had more rapid relief after administration of nitroglycerin (Table III). Seven of the 8 had 3 vessel disease, and 1 had 2 vessel involvement. Six had abnormalities of left ventricular wall motion, 2 with associated hemodynamic abnormalities. One patient with normal wall motion had abnormal hemodynamics.

Four patients with coronary artery disease (8 percent) reported that nitroglycerin did not affect the chest pain. Of these, 1 reported that the drug had effectively alleviated his pain several years before but had gradually lost its efficacy. Another reported that shortness of breath, which usually accompanied the pain, was relieved by nitroglycerin, although the pain itself was not. Three of these patients had obstructive lesions in all 3 major arterial systems and hemodynamic and left ventricular wall motion abnormalities. All 3 were subject to several attacks of angina daily and experienced pain with minimal activity. The fourth patient in this group had 75 percent narrowing of the main left coronary artery, the only lesion of this vessel in the study, and was classified as having 2 vessel disease.

Most subjects reported that pain of all types—whether they occurred on exertion, after meals, nocturnally, at rest or in association with emotional stress—were equally well relieved by nitroglycerin. When, as in a few patients, the pains were not abolished, the episodes were unusually severe and occurred most commonly either nocturnally or while the patient was undisturbed at rest. Exertional pain was almost always readily relieved. Patients with a delayed response to nitroglycerin were more likely to fail occasionally to obtain relief than those who usually gained prompt benefit.

There were no statistically significant differences in incidence of collateral vessels among the various groups (Table III). However, all 14 patients with 3 vessel disease who had a prompt response to nitroglycerin had collateral vessels, whereas 2 patients with a delayed response and 1 with no response had 3 vessel disease without collateral vessels.

Seven patients reported that if they delayed in taking nitroglycerin after pain began, there was

TABLE II

Response to Nitroglycerin and Presence of Coronary Artery Disease

	Patients With Coronary Artery Disease (no. = 49)		Patients Without Coronary Artery Disease (no. = 21)	
	no.	%	no.	%
Prompt relief*	37	76	4	19
Delayed relief	8	16	9	43
Absent or equivocal relief	4	8	8	38
Severe side effects†	7	14	9	43

* Prompt relief = less than 3 minutes; † severe side effects = intense long-lasting headaches, dizziness, syncope or other phenomena that caused severe discomfort. Mild brief headaches are not included.

TABLE III

Response to Nitroglycerin and Extent of Coronary Disease

Catheterization Findings	Prompt Relief* (37 Patients)		Delayed Relief (8 Patients)		No Relief (4 Patients)	
	no.	%	no.	%	no.	%
3 vessel disease	14	38	7	88	3	75
2 vessel disease	18	49	1	12	1	25
1 vessel disease	5	13	0	0	0	0
Hemodynamic abnormalities†	8	22	3	38	3	75
Left ventricular asynergy‡	13	35	6	75	3	75
Collateral vessels§	30	81	6	75	2	50

* Prompt relief = less than 3 minutes for total or substantial relief of chest pain; † hemodynamic abnormalities = elevated ventricular end-diastolic pressures or low cardiac output; ‡ left ventricular asynergy refers to abnormalities of left ventricular wall motion as defined in the text; § collateral vessels = abnormal channels visible on coronary arteriograms.

an appreciable interval before the pain was allayed, as compared with instances in which they took the medication immediately. However, 31 others could recognize no difference in effectiveness or time required for relief whether they took nitroglycerin immediately or after a delay of several minutes. The remaining 32 patients habitually took their medication immediately and were unable to answer this question.

Effect of nitroglycerin in patients without coronary disease: In this group the coronary vessels were either completely normal or had no stenosis constricting the lumen by more than 30 percent. No hemodynamic or wall motion abnormalities were detected. Four patients (19 percent) usually obtained relief within 3 minutes after taking nitroglycerin for pain (Table II). Nine patients (43 percent) experienced relief only after intervals in excess of 3 minutes, usually 5 minutes or more. Six patients (29 percent) reported that nitroglycerin was never effective.

Two patients occasionally had prompt relief of pain but often found nitroglycerin to be ineffective. One reported that pain with exertion was often not relieved, although nonexertional pain, which he sometimes experienced, was always relieved. The other was unable to describe, in terms of precipitating cause or intensity of pain, when the drug was ineffective.

Side effects of nitroglycerin: Twenty-four of the patients with coronary disease (49 percent) regularly experienced headaches after taking nitroglycerin. Ten others (20 percent) did not have headaches at the time of the study but recalled having had headaches when they first began therapy with nitroglycerin. The headaches ranged from barely noticeable to severe and were usually described as a "throbbing" or "pounding" sensation localized to the frontal or temporal regions and bilateral. Headaches usually lasted approximately 5 minutes and seldom lasted more than 20 minutes. One patient with coronary disease experienced an episode of syncope while at stool after taking a nitroglycerin tablet. Three patients with coronary disease reported rare episodes of dizziness with the drug.

Seventeen of the patients without coronary disease (81 percent) were subject to headaches after nitroglycerin. Two others (10 percent) had previously experienced headaches. Nine of the patients without coronary disease (43 percent) reported unusual side effects (Table III). Four regularly experienced severe, disabling headaches that often lasted several hours. Recurrent dizziness after taking nitroglycerin was reported by 1 patient. One subject had 2 syncopal episodes and recurrent dizziness. One subject discontinued the drug because it induced nausea and eructation. One reported an episode of severe back pain after taking the drug. One associated the drug with an incident in which an arm suddenly felt cold and began to shake uncontrollably.

Several patients in the groups with and without coronary disease who did not usually experience severe headaches with glyceryl trinitrite (nitroglycerin) were unable to tolerate long-acting nitrite or nitrate preparations because of severe headaches.

Effects of other drugs, age, sex and duration of therapy on response to nitroglycerin: Thirty-one patients with coronary artery disease and 5 without disease had taken orally or sublingually administered long-acting nitrites or nitrates. Thirty patients with disease and 2 without disease had taken propranolol in doses ranging from 80 to 160 mg/day. No patient reported any alteration in his response to nitroglycerin while receiving these drugs.

Neither age nor sex appeared to be related to the nature of the response to nitroglycerin in patients with or without coronary artery disease. Duration of therapy was also not clearly related to response to nitroglycerin. Although a few patients who had been taking nitroglycerin for many years appeared to have decreased responsiveness to the drug, others reported consistent prompt relief despite long-term usage and an unchanged dosage of 0.3 or 0.4 mg.

Discussion

The physiologic actions of nitroglycerin were first systematically investigated by Brunton and Tait[9] in 1876. Use of the drug as a remedy for angina pectoris was reported by Murrell[1] in 1879. In his lectures on therapeutics published in 1903, Brunton[10] postulated that nitroglycerin and amyl nitrite were specific antagonists for anginal pain. Subsequently, nitroglycerin has proved to be so consistently efficacious in angina pectoris that response to the drug is of diagnostic as well as therapeutic value.[2]

The clinical diagnosis of coronary artery disease with angina pectoris is frequently based on the history furnished by the patient. It is difficult to distinguish by this means patients with coronary artery disease from those patients who complain of chest pain of the anginal type but do not have angiographically demonstrable coronary lesions. Since inquiry as to the effectiveness of nitroglycerin in relieving symptoms is an essential portion of the history, it is of practical value for the clinician to be aware of the range of subjective responses to the drug and the correlation of these responses with the presence or absence of obstructive coronary artery disease in a population with recurrent nonpleuritic chest pain.

Response to nitroglycerin proved to have discriminatory value in identifying the patients with coronary artery disease. Consistent relief of pain

in less than 3 minutes was common in patients with coronary artery disease but infrequent in those with angina-like pain but no demonstrable cardiac disease. In the population studied, 90 percent of those who exhibited a prompt response to nitroglycerin had coronary artery disease.

Lack of response to nitroglycerin or relief of pain only after prolonged periods of time occurred in patients with or without coronary disease. An absent or delayed response in patients with relatively infrequent or mild angina was associated with absence of detectable abnormalities. In contrast, patients with coronary artery disease and infrequent episodes of pain almost always experienced prompt and complete relief with nitroglycerin. Sporadic failures to relieve pain were encountered in patients with frequent severe angina. In such patients, nocturnal pain or pain at rest without obvious precipitating cause was most likely not to be relieved, but response was usual when the pain was associated with exertion. The higher incidence of hemodynamic and wall motion abnormalities in patients with absent or delayed responses presumably reflects more serious coronary obstructive disease and possibly, in some cases, poorer collateral flow to diseased regions.

Headaches due to nitroglycerin were common in patients with or without disease, especially when first taking the drug. The headaches were usually mild and brief. Complaints of very severe or long-lasting headaches, syncope or bizarre reactions were usually associated with absence of disease.

The pattern that emerges of the patient without detectable disease is one of delayed or absent responsiveness to nitroglycerin and a tendency to complain of severe or odd side effects. Patients with coronary artery disease usually respond promptly to nitroglycerin and seldom complain of side effects. However, in an occasional patient with severe coronary disease the drug is ineffective, and there is delayed or absent responsiveness similar to that encountered in patients without disease, although the tendency to unusual side effects is lacking.

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Natural History of Angina Pectoris in the Framingham Study

Prognosis and Survival

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The evolution of 303 cases of angina in a general population sample of 5,127 persons was ascertained and revealed that the lot of the angina victim is not a happy one. Prognosis as to survival and progression to more serious coronary manifestations was discouraging in men. One in 4 men with angina can expect to have a coronary attack within 5 years. The risk is half this for women. About 30 percent of those over 55 will die within 8 years, and 44 percent of the coronary deaths will be sudden. Mortality was close to that which follows the posthospital phase of myocardial infarction. Surprisingly, survival in men with uncomplicated angina was no better than that for angina which follows an infarction.

Angina was more likely to be the presenting complaint of coronary disease in women (65 percent) than in men (37 percent). In men 45 percent of angina arose out of myocardial infarction compared to 15 percent in women. Half of those sustaining initial myocardial infarctions had angina following it, 31 percent experiencing it for the first time. In those with angina who sustained an infarction, the angina disappeared in only 15 percent of men and no women, a rate lower than the 30 percent spontaneous rate of disappearance. Only 23 percent of infarctions were preceded by angina. Almost 1 in 4 myocardial infarctions were silent or went unrecognized. Such infarctions were rare in persons with prior angina.

Most previous studies of the natural history of coronary heart disease in general and angina pectoris in particular have been handicapped by an inability to obtain samples of patients which are representative of the total disease experience. The Framingham study has been able to a great extent to overcome this difficulty by following a large random sample of the general population, documenting all evidence of coronary heart disease obtainable from a comprehensive medical surveillance of the population including biennial cardiovascular examination, review of hospital and physician's records, medical examiner's reports and death certificates. The purpose of this report is to explore the conditions under which angina pectoris arises, evolves, becomes complicated by more serious manifestations of atherosclerosis and terminates fatally.

Methods

The data to be presented were obtained as part of the National Heart and Lung Institute's Framingham Heart Study, which has been described in detail elsewhere.[1-4] Briefly, the Framingham study has been following up a cohort of 5,209 persons, initially examined from 1949 to 1952, by means of biennial cardiovascular examinations up to the pres-

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ent time. This report is concerned with 14 years of follow-up experience in the cohort of the 5,127 persons who were found free of clinical manifestations of coronary heart disease at the time of initial examination.

The follow-up for death has been gratifyingly complete, with less than 2 percent of subjects lost after 14 years of medical surveillance. Follow-up for angina is somewhat less complete but still adequate since 85 percent of survivors have returned for every biennial examination. Furthermore, many of those who did not appear for the eighth biennial examination were seen at a later examination. Also, hospital records were available if the patient had been hospitalized for a cardiovascular complaint in the interim between examinations.

Diagnostic Criteria

The clinical criteria employed for the diagnosis of the various manifestations of coronary heart disease have been reported in detail previously[1–4] and are summarized briefly here.

Angina pectoris was diagnosed when symptoms of substernal distress of short duration (less than 15 minutes), distinctly related to exertion or excitement and relieved by rest or nitroglycerin, were elicited from the subject who also often complained that the discomfort radiated into the arms or neck. When another possible explanation was present or the discomfort also occurred as often at rest, the diagnosis was rejected. All suspected cases were reviewed by another examining physician at the time of the clinic visit, and his opinion was also obtained. Interviews to elicit the symptoms were structured, requiring the physician to go through a standard series of queries which included the presence, location and nature of the complaint, factors that precipitated it, its duration (usual and longest), radiation of the discomfort, its frequency and factors that relieved it. In addition to the 2 examiners' opinions, each suspected case was also reviewed by a panel of investigators who made the final diagnostic determination independent of knowledge of the person's living habits or personal characteristics. Electrocardiographic abnormalities either at rest or with exertion were not required for the diagnosis.

Myocardial infarction required the demonstration of evolution of unequivocal changes of myocardial infarction on the electrocardiogram when compared to previous tracings, or diagnostic elevation of serum enzymes indicating muscle necrosis, or both, in a clinical setting of ischemic chest pain of prolonged duration. All hospital protocols were reviewed by a panel of investigators. The appearance of unequivocal electrocardiographic evidence of muscle necrosis since the last biennial visit by comparing the 2 electrocardiograms was accepted as an unrecognized infarction when no interim symptoms had occurred or when atypical symptoms were present and regarded by neither the attending physician nor the victim as a possible coronary attack.

Sudden unexpected death was diagnosed when death occurred under circumstances suggesting a matter of minutes from onset to termination and was documented to have occurred in under 1 hour, in persons suffering from no lethal disease and when no other explanation for the death was available.

The coronary insufficiency syndrome was diagnosed when a clinical history suggesting a myocardial infarction was obtained but no evidence of muscle necrosis either on electrocardiogram or serum enzymes could be demonstrated. Transient ischemic electrocardiographic changes during hospitalization were required for this diagnosis.

In this report the few cases of angina resulting from other causes than coronary atherosclerosis (for example, hyperthyroidism, anemia, aortic stenosis and regurgitation, syphilitic heart disease) have been excluded. The intention was to study atherosclerotic angina pectoris, which in the general population accounts for the vast bulk of angina. Also, in these other types of angina it is difficult to separate the prognosis associated with the angina from that contributed by the underlying disease.

Methods of Analysis

Life-table analysis was employed to determine survival and probability of another event of coronary heart disease. Because of the difficulty in dating the precise onset of angina pectoris, it was decided to use the midpoint of the examination interval in which the diagnosis was made as the date of onset. The status of each patient was then ascertained at the first anniversary of the onset of angina and each biennial anniversary thereafter. The formula used to calculate the probability of dying, q_i, during the i'th interval after the onset of illness, given that the subject was alive at the beginning of the interval, is $q_i = d_i/1_i$, where d_i = number of deaths during the interval, and 1_i = number of patients alive at beginning of the interval and followed during the interval.

All withdrawals occurred at an anniversary so no corrections were needed in the formula for these cases.

Relative mortality was calculated for each specified age group in each sex by determining the ratio of observed to expected deaths. The expected number of deaths for each age-sex group was computed as follows: let p_i be the proportion in a particular age-sex group surviving from examination i to i + 1 (i = 1, 2----7), let $P_i = p_i$ to $p_i + 1$----P_7, and n_i be the number of persons of the specified age and sex first appearing with the specified manifestation of coronary heart disease at examination i; then $\Sigma n_i (1 - P_i)$ is the expected number of deaths. Thus, age-adjusted mortality ratios were obtained for persons with angina and myocardial infarctions in comparison to the standard or average mortality of the entire cohort of 5,127 persons with the average risk of death set at 100.

The probability of a second event of coronary heart disease in persons with angina was calculated by life table methods for variable periods of follow-up by the method of Chiang[5] in which mortality from all other causes is treated as the competing risk. This multiple decrement procedure permits the calculation of "net" rates of morbidity.

Results

During the course of 14 years of biennial cardiovascular surveillance at the Framingham study 492 persons had for the first time clinical evidence of coronary heart disease. Angina pectoris was

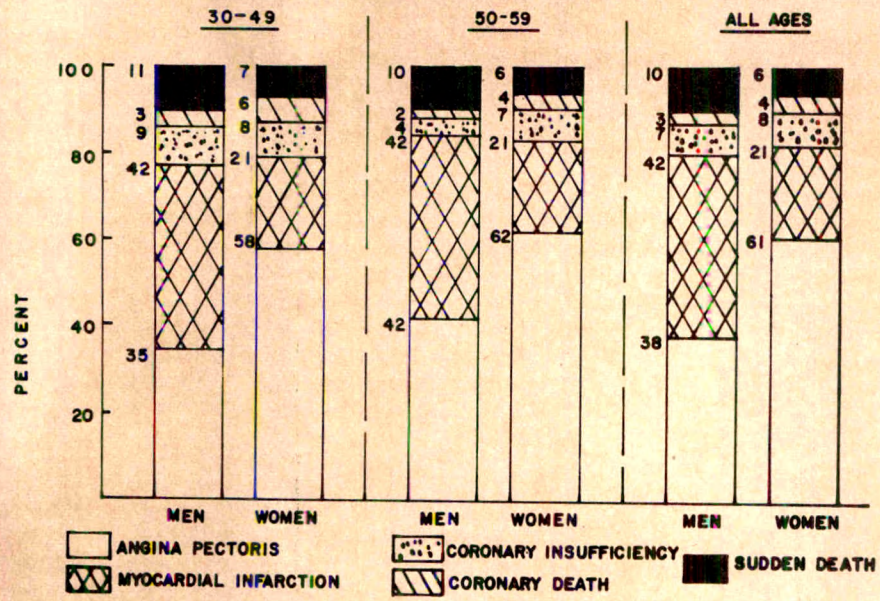

Figure 1. Presenting clinical manifestation of coronary heart disease. Men and women aged 30 to 62: Framingham study.

clearly a common clinical expression of the disease. Among the 323 men who had coronary heart disease, 119 (36.8 percent) first presented with angina pectoris. A much higher proportion of the 169 women with coronary heart disease, 110 (65.1 percent), presented with this symptom. Thus, there is a distinct difference in the way coronary heart disease presents in the 2 sexes. The distribution of clinical manifestations of coronary heart disease did not vary significantly with age (Fig. 1).

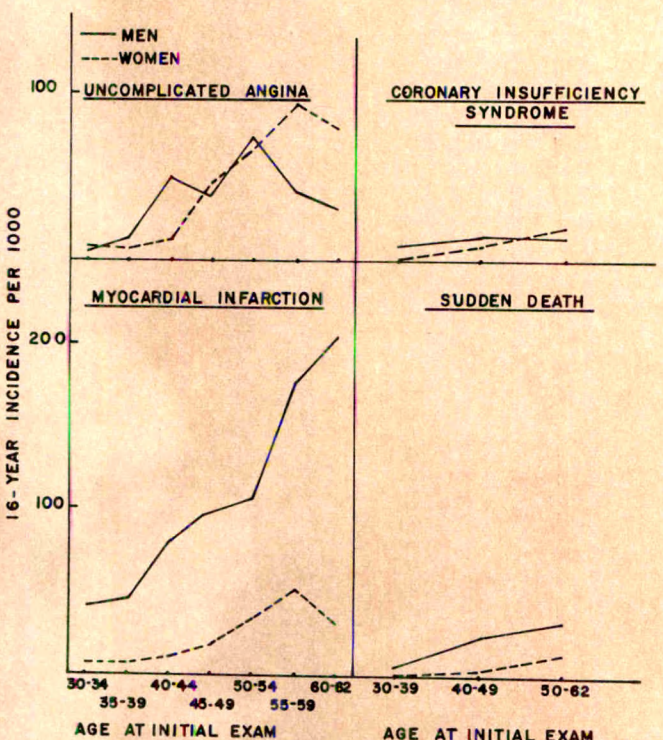

Figure 2. Sixteen-year incidence of manifestations of coronary heart disease according to age in each sex. Men and women aged 30 to 62 at entry:Framingham study.

An examination of the incidence rates reveals a distinct male predominance of the various forms of coronary heart disease. Women lag behind men some 20 years in incidence of myocardial infarction and sudden death (Fig. 2). Angina as a presenting complaint of coronary heart disease was also more frequent among men, with a gap of about 10 years in incidence between the sexes, the gap closing with advancing age (Fig. 3). However, uncomplicated angina was about as frequent in women as in men (Fig. 2). At younger ages it was less frequent in women than in men but at older ages the sex ratio was reversed.

Types of Angina

This suggests that there may be at least 2 forms of angina which have different epidemiologic features. Angina may arise de novo in persons who have never had any other clinical expression of coronary artery disease. It may also arise contiguous with, or as a consequence of, a myocardial infarction. In such persons it may develop as a premonitory symptom of an impending myocardial infarction, or it may become manifest when they attempt to return to their accustomed level of physical activity after infarction. To analyze the epidemiologic features of angina and its natural history in more detail, the total of 303 cases of angina arising in the population sample were divided into 3 types of anginal events: (1) uncomplicated angina, in which the symptom was the initial manifestation of coronary heart disease and in which a myocardial infarction or the coronary insufficiency syndrome or coronary death did not occur in the same examination interval; (2) complicated angina, in which angina developed along with a myocardial infarction, coronary insufficiency or coronary death in the same examination

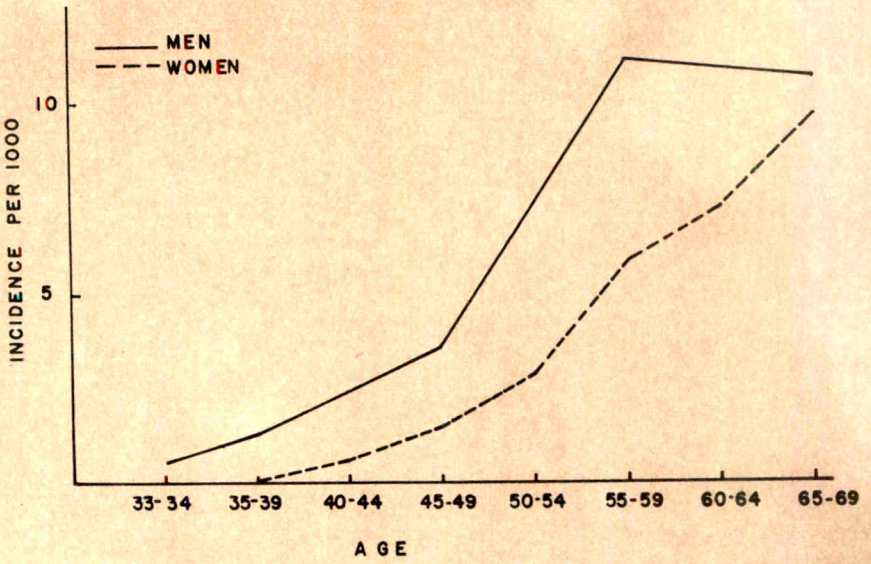

Figure 3. Smoothed average annual incidence of angina pectoris as a presenting complaint. Men and women aged 33 to 69: Framingham study.

interval; and (3) angina following myocardial infarction after at least 1 biennial examination interval. Among the men 53 percent of the angina was of the uncomplicated variety, whereas 37 percent of cases occurred contiguously with myocardial infarction. Only 10 percent arose sometime after a myocardial infarction. In women, the picture was quite different with more than 85 percent of cases of the uncomplicated type; only 15 percent occurred together with or subsequent to a coronary attack (Fig. 4).

Occurrence of Angina in Persons with Myocardial Infarction

Angina pectoris is a common sequela of myocardial infarction. Half of those sustaining an initial myocardial infarction had angina after it. However, only 31 percent experienced it for the first time after their myocardial infarction, the remaining 18 percent had it before the myocardial infarction and simply continued to have it (Fig. 5).

Postinfarction angina: Angina tends to be a persistent complaint even after an overt myocardial infarction. Among persons presenting with angina pectoris, there were 29 men and 8 women who subsequently had a myocardial infarction and survived long enough to return for reexamination. Only 4 of the 29 men (15 percent) experienced no further angina in the period of follow-up after their infarction; angina did not disappear in any of the women. This rate is lower than the spontaneous rate of loss of angina (30 percent) without intervening infarction. This does not support the contention that an infarction may cure angina by making the ischemic myocardium necrotic.[6]

Unrecognized myocardial infarction: Myocardial infarction more often than not occurs without warning in unsuspecting victims free of prior symptoms of any duration. Only about 23 percent of attacks were preceded by angina pectoris. Unrecognized infarction in particular was distinctly uncommon in persons who had prior angina. The proportion with unrecognized myocardial infarc-

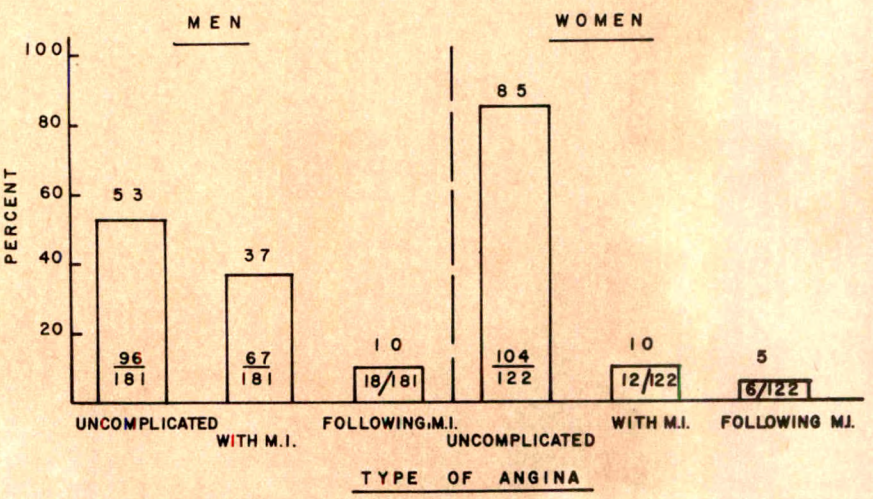

Figure 4. Frequency of angina pectoris by type. Men and women aged 30 to 62 at entry: Framingham study.

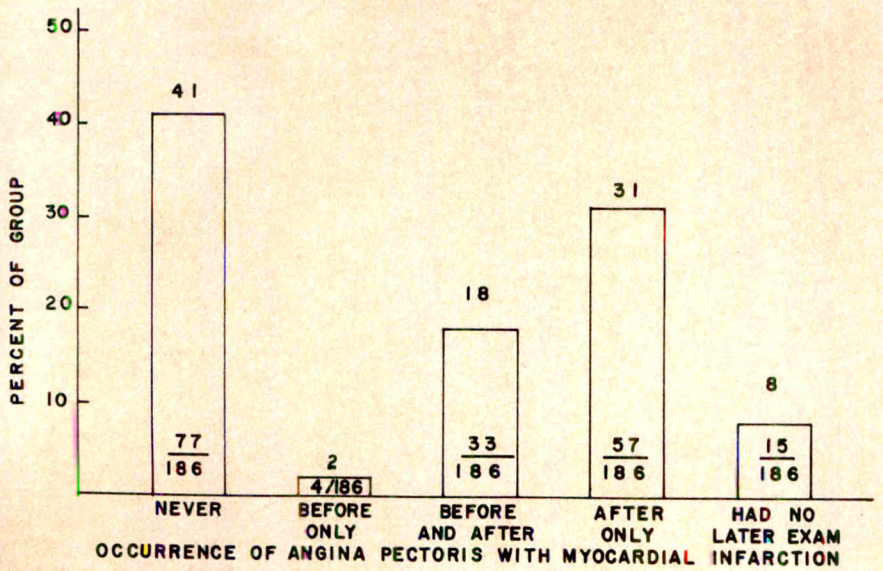

Figure 5. Occurrence of angina pectoris in subjects surviving initial myocardial infarction 3 weeks or more. Men and women aged 30 to 62 at entry: Framingham study.

tion was 5 times as great in those without angina as in those with it (Table I). This does not necessarily reflect unusual sensitivity to ischemic pain in those with angina since it could also be the result of a heightened level of suspicion in those with previous angina. The rate of occurrence of angina *after* a myocardial infarction does reflect directly on the issue of sensitivity to ischemic cardiac pain since even unrecognized myocardial infarctions diagnosed at the Heart Program were routinely reported to the victim's physician. Persons with unrecognized myocardial infarction had subsequent anginal distress somewhat less frequently than those with symptomatic myocardial infarction, but the difference was less dramatic (Table I). This suggests that most unrecognized myocardial infarctions probably represent overlooked atypical symptoms rather than truly painless infarctions.

TABLE I

Angina and Myocardial Infarction in Men and Women Aged 30 to 79 Years

A. Proportion of Myocardial Infarctions Followed by Angina Pectoris*

Type of MI	Subjects (no.)	MI Followed by AP* no.	MI Followed by AP* %
Unrecognized	41	13	32
Recognized	81	41	51
Total	122†	54	44

B. Proportion of Myocardial Infarctions Unrecognized According to Antecedent Angina Status

Prior AP	Subjects (no.)	Proportion Unrecognized MI* no.	Proportion Unrecognized MI* %
Present	39	2	5
Absent	149	42	28
Total	188	44	33

* Differences significant at $P < 0.01$ level, sex-specific.
† Excludes persons with prior angina pectoris.
AP = angina pectoris; MI = myocardial infarction.

Clinical Course of Patients Presenting with Angina

Examination of the subsequent status of persons presenting with angina pectoris as their initial manifestation of coronary heart disease reveals that this is far from an innocuous cardiovascular complaint. Among the 119 men first presenting with angina pectoris, 33 (28 percent) died. Of those who presented with angina, 52 of 119 (44

TABLE II

Angina Pectoris and Other Forms of Coronary Heart Disease in Persons Initially Free of Coronary Heart Disease: Framingham Study, 14 Year Follow-Up

Initial Event	Status at 14 Years	Men (no.)	Women (no.)
AP	Alive, no other CHD	62	83
	Alive, with other CHD	24	13
	Dead, no other CHD	5	8
	Dead, had other CHD	28	6
	Total	119	110
Other CHD	Alive, no AP	61	18
	Alive, had AP	47	10
	Dead, no AP	81	29
	Dead, had AP	15	2
	Total	204	59
Total AP		181	122
Total CHD		323	169

AP = angina pectoris; CHD = coronary heart disease.

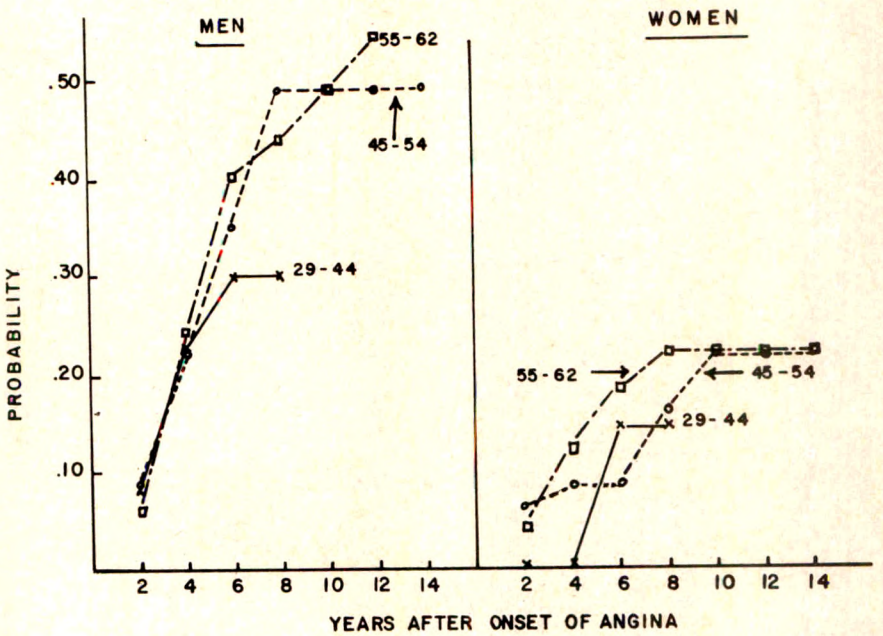

Figure 6. Probability of a coronary attack in persons with angina pectoris. Men and women aged 30 to 62 at entry: Framingham study.

percent) men and 19 of 110 (17 percent) women later had some other more serious manifestation of coronary heart disease. Again, women appeared to have a better prognosis than men (Table II).

The probability of a coronary attack within 8 years after the onset of angina pectoris is about 50 percent in men over 45 years, a relative risk double that of the general population (Fig. 6). The probability is lower in women. Although the absolute risk increases with age, there is a suggestion that the relative risk diminishes with advancing age.

Other complications of atherosclerosis: Angina victims were at high risk of other atherosclerotic disease outcomes in addition to coronary heart disease. The outcome that resembles it most closely—intermittent claudication of the calf muscles on exercise due to occlusive arterial disease—occurred almost 3 to 5 times as commonly among patients with angina as in those without coronary heart disease, taking age and sex into account (Table III).

Atherothrombotic brain infarctions and congestive failure occurred too infrequently in the period of follow-up available to obtain reliable estimates of the probability of their occurring in patients with angina.

Mortality

Survival patterns for men and women with angina pectoris calculated by the life table method reveals definitely impaired survival compared to the general population with no definite age trend in men. In both men and women angina pectoris before age 50 years was relatively rare and among the 24 cases occurring prior to this age there was only 1 death. Therefore, it cannot be definitely stated that there is any increased risk of death associated with angina pectoris in persons who had it at a young age. This must be interpreted cautiously since the numbers of events is so few. In younger women (under 60 years) with uncomplicated angina, survival appeared to be better than in men or older women (Fig. 7). In men with uncomplicated angina, age did not appear to influence survival. Within 8 years 40 percent of all the men and of the older women died, whereas only 15 percent of the women under age 60 died (Fig. 7).

TABLE III

Incidence of Intermittent Claudication According to Presence of Uncomplicated Angina Pectoris* at Examination, by Sex and Age: Framingham Study, 14-Year Follow-Up

Sex & Age (yr) at Examination	Average Annual Rate per 10,000		Relative Risk
	Without CHD	With AP	
Men	19	96	2.8†
30–44	5	0	...
45–54	15	65	4.2
55–64	44	120	2.7
65–74	26	100	3.8
Women	10	115	5.2†
30–44	3	0	...
45–54	6	83	14.1
55–64	15	103	7.0
65–74	46	176	3.8

* Uncomplicated angina pectoris (AP) is angina pectoris as the only evidence of definite coronary heart disease (CHD) at beginning of examination interval.

† Age-adjusted by indirect method using as standard rates the sex-age-specific incidence rates (in 5-year age groups) for the entire study.

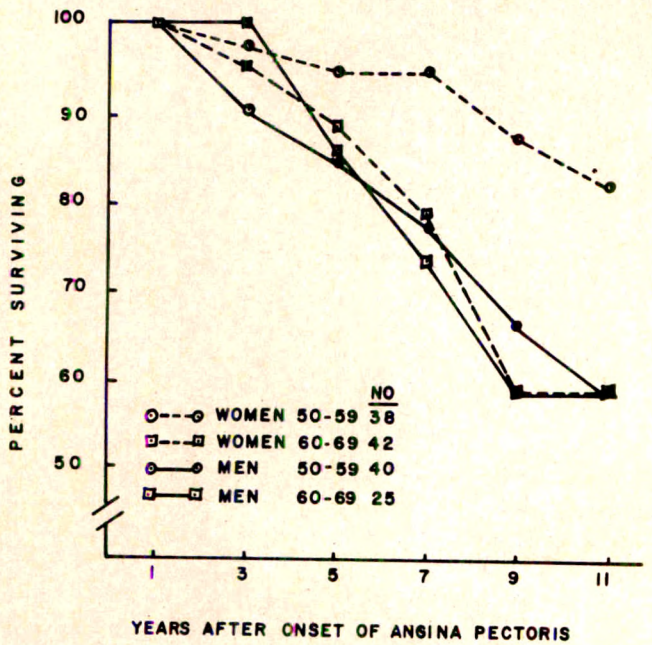

Figure 7. Survival after uncomplicated angina pectoris. Men and women aged 50 to 69: Framingham study. Uncomplicated angina indicates angina without myocardial infarction or acute coronary insufficiency as initial event and survival to next clinic examination.

Surprisingly, survival in men with uncomplicated angina was no better than survival following the acute stage of an infarction in those persons having their angina contiguously with a myocardial infarction, that is, "complicated angina" (Fig. 8). Thus, on the whole, angina in men was attended by about a 4 percent mortality per year, whether it arose de novo or in conjunction with a myocardial infarction (Fig. 9).

Examination of the probability of death in angina victims, excluding those with other manifestations of coronary heart disease prior to death, reveals a mortality surprisingly close to that which follows the posthospital phase of a myocardial infarction. Adjustment for the high immediate mortality associated with myocardial infarction is made by including only those patients who have survived at least 1 year after their myocardial infarction. By the end of 8 years after the examination at which either of these coronary manifestations was diagnosed, about 30 percent in the age group 55 to 64 years (where numbers are adequate to judge) had died (Fig. 10).

Sudden death: This accounted for 44 percent of all coronary deaths in persons with angina. The proportion of sudden deaths in patients with angina did not appear to vary with age, but numbers were too small to reliably evaluate the impact of age on suddenness of coronary death. Numbers were also too small to determine whether sudden death was more common in complicated than in uncomplicated angina.

Discussion

Sir James MacKenzie pointed out that accurate prognostication was even more difficult than arriving at a correct diagnosis.[7] He recognized that it required a detailed knowledge of the natural history of the disorder in question. Although clinical experience with angina pectoris has been quite extensive, prognostication has remained rather uncertain owing to incomplete subsamples of the disease followed up in an unsystematic fashion with the data often inappropriately analyzed. It is hoped that the present study has overcome some of these problems.

The prognosis in angina pectoris has been extensively reported in numerous publications and texts.[5,7–14] Such reports, while they may accurately portray the expectation of life and the clinical course of angina in special subgroups of angina patients under medical surveillance for one reason

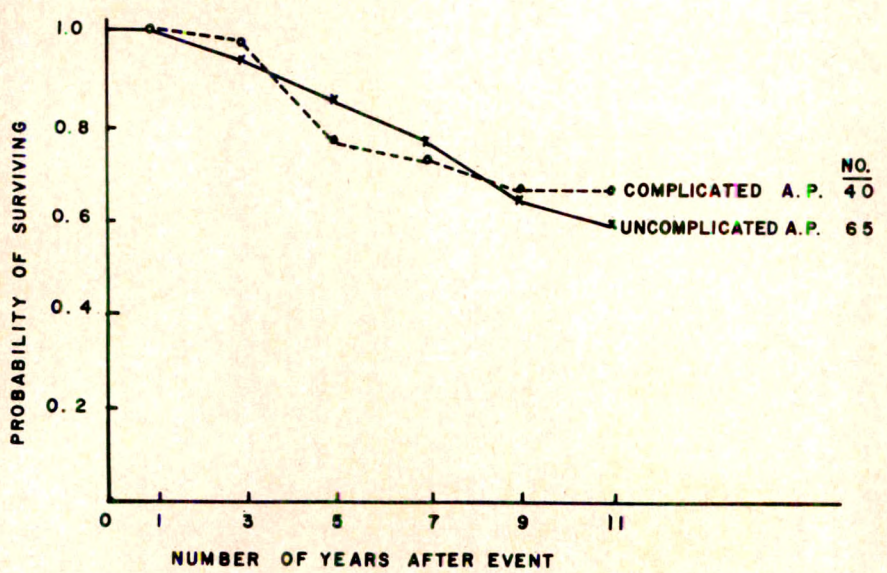

Figure 8. Probability of surviving after diagnosis of angina pectoris. Men aged 50 and over: Framingham study.

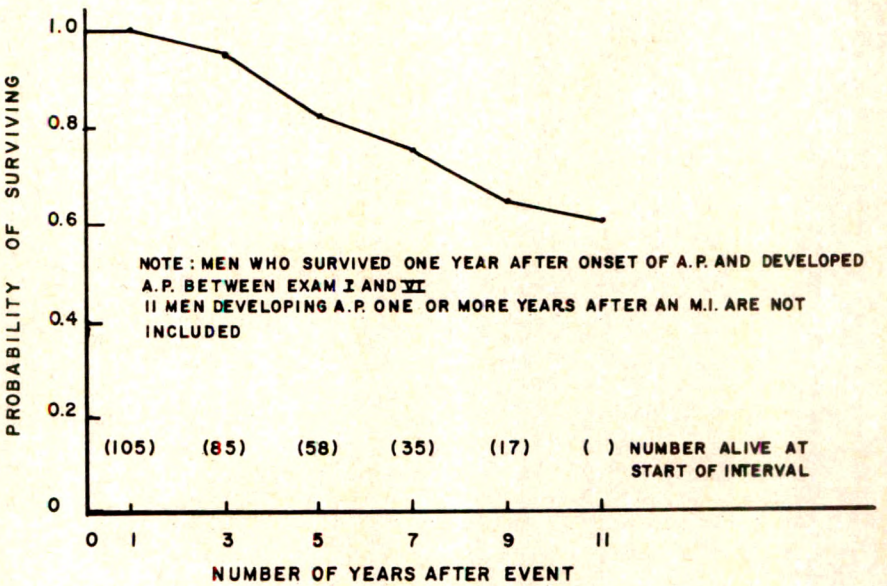

Figure 9. Probability of survival after diagnosis of angina pectoris (complicated and uncomplicated combined). Men aged 50 and over: Framingham study.

or another, may not reflect the natural history of the disease in the general population. Only by examining its natural history in the general population, including those cases arising shortly before a myocardial infarction and sudden death and those too mild to come under medical attention for prolonged periods, can an undistorted appreciation of the entire clinical spectrum of angina be achieved. Paul[14] and Hurst and Logue[15] suggest quite logically that the true prognosis in angina may be more favorable than commonly reported on the basis of data compiled by cardiologists seeing patients often referred for severe symptoms. However, those rapidly culminating in sudden death may not reach them either.

Survival rates: White et al[8] reported in 1943 that 90 percent of 500 patients died after an average period of 8 years after onset of symptoms. In a later study encompassing 25 years of follow-up at which time 445 of 456 were dead, the average survival was 9.7 years.[9] It is clear that "average survival" statistics make sense only if the entire cohort is followed to death since the average survival must increase in proportion to the length of follow-up. In a larger follow-up series of 6,882 cases, more appropriately analyzed, about 15 percent died within 1 year of onset, and thereafter the average annual mortality was reported at about 9 percent. The 5 year survival rate was 58.4 percent compared with 87 percent for the general population.[10]

It is widely recognized that angina of recent onset, that which has changed recently in severity or ease of provocation and angina at rest, carries a poor prognosis. Such unstable angina may be premonitory to a myocardial infarction or sudden death.[7,13] It is possible that some of these cases may have gone undetected in this study of the

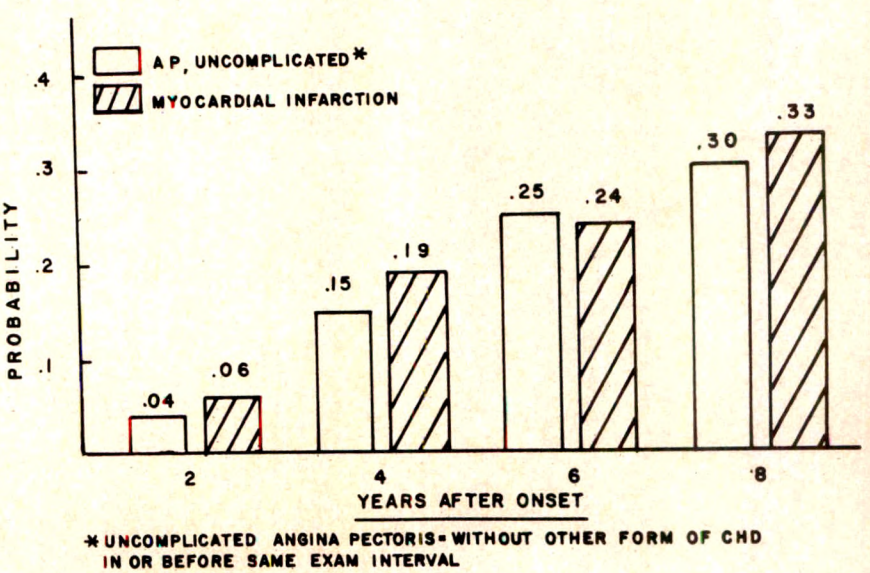

Figure 10. Probability of death according to coronary heart disease (CHD) status. Men aged 55 to 64: Framingham study.

Framingham population, while fairly complete reporting of mild angina, including that of subjects not under medical care, is likely to have been achieved. This could result in some underestimate of the seriousness of angina.

Probability of myocardial infarction: Estimates of the probability of a myocardial infarction in patients with angina have also been subject to possible error. Friedberg[7] points out that at least 25 percent of patients with angina will have 1 or more myocardial infarctions before death. This is likely to be an underestimate. Studies at Framingham indicate that at least 1 in 5 myocardial infarctions in the general population are silent or go unrecognized at the time of occurrence.[15] Although this is less likely in patients with angina, some do escape detection at the time of the event (Table I). Also, it is commonly believed that a sharp increase in the severity and frequency of anginal attacks strongly suggests that occlusion of a large coronary vessel has taken place whether or not signs of a myocardial infarction can be elicited. The appearance of congestive heart failure is also likely to reflect closure of additional vessels and extension of myocardial damage if not due to associated hypertension.[12] About 1 in 4 men with angina can expect to have a myocardial infarction within 5 years, half of those over 45 years of age within 8 years, a figure somewhat higher than the estimate of Friedberg.[7] This is a relative risk about double that of the general population the same age.

Sudden death: It has long been recognized that angina patients are unusually prone to sudden death. Harrison and Reeves[13] point out that "there is no other common disorder in medicine in which prognosis is so uncertain, because there is no other in which an individual, while carrying on normal activity and apparently in the best of health, is so likely to die suddenly." About 45 percent of all deaths from coronary disease in angina subjects were sudden, a proportion similar to that for victims of myocardial infarction and no different from that of persons who die of coronary heart disease without prior evidence of such disease. The incidence of sudden death, on the other hand, is distinctly higher in angina patients, by more than 3-fold, than in the general population. More information is needed concerning the type of patients with angina particularly liable to sudden death and the predisposing factors.

Disappearance of angina: It is recognized that angina may disappear spontaneously for long periods, even permanently, after it has been present for years. This has been attributed to the development of collateral circulation or to the replacement of an ischemic area of myocardium by scar tissue following coronary occlusion.[7] The latter must not occur very often since it is clear from this study that the disappearance of angina for long periods occurs no more often after a myocardial infarction than it does spontaneously without an intervening infarction. In fact, an intervening myocardial infarction seems to favor persistance of angina, presumably reflecting a more compromised coronary circulation. Loss of angina reported to occur after onset of congestive failure and atrial fibrillation may well be the result of enforced limitation of physical activity.

Disability from angina: Although angina can cause severe disability and chronic invalidism, most victims are very little inconvenienced and are capable of carrying on most of their usual business activities.[7] Nevertheless, evaluation of the evolution of angina pectoris as it occurs in the general population reveals that the lot of the angina victim is not a happy one. In addition to the painful disability and resultant restriction of activity, the prognosis as to survival and progression to a more serious clinical manifestation of the disease is in men rather discouraging.

Sex and age: It has been alleged that women with angina have a better prognosis than do men and that those over age 40 years at onset fare better than younger women.[11] The data from Framingham appear to support this contention. In both sexes the absolute risk of a myocardial infarction increases with age. However, relative risk—that is, compared to other persons without angina of the same age—decreases with age.

Among persons with coronary heart disease chances of surviving an extended period are better at younger than older ages. In women the chances are better than in men. Uncomplicated angina is a very serious condition in men, with the mortality being about 5 percent per year; in women it is only half this and approximates that of women in general. The disparity between the sexes increases with the passage of time, the rates being quite similar during the first 5 years after onset.

While angina poses only a modest threat to survival in women, it has implications in men, as regards survival, no less ominous than that for victims surviving the acute period of a myocardial infarction. The rate of survival for 1 decade is only half that expected for men the same age.

Comparison with other reported studies: These findings in Framingham compare reasonably well with clinical series of angina patients. Richards and co-workers,[9] who followed up 456 subjects with angina (average age 57 years) for at least 25 years, noted a 5 year survival rate of 64 percent for men and 74 percent for women and, after a decade, 41 percent survival for men and 44 percent for women. The somewhat lower rates could be due to the inclusion of complicated angina or sicker patients requiring medical management. However, the study also revealed a higher mortality in men than women and a *relative* survival which was the same in young and old, although *absolute* survival decreased with age.

These findings of a *relative* survival unaffected by age and better survival experience in women was also confirmed by Block et al.[10] in 6,882 cases of angina. The survival experience in this large series of cases was roughly comparable to that of the other large clinic series. Feil et al.[16] in a meticulous study of 338 cases of angina followed up for 20 years found a similar survival experience.

In a careful study of military personnel Zukel et al.[17] found a somewhat lower average annual mortality (3 percent) beginning 1 year after diagnosis in persons with angina. This better experience may be due to the younger age of the sample and the absence of other major complicating illness among these military personnel. The relative mortality was also found to be lower in older subjects; however, they found a higher average annual mortality after the first year (5 percent) in the myocardial infarction than angina cases.

It thus seems reasonably clear that angina is less serious in women than men, and that the absolute survival rate declines with age. However, although absolute mortality increases with age, angina seems to impose the same load of excess mortality on the young as the old relative to their respective cohorts without angina.

Clinical implications: A good deal of attention is justifiably given to relieving symptoms and increasing exercise tolerance in the angina patient. However, even more important is secondary prevention aimed at reducing the high likelihood of a myocardial infarction and premature death. Information concerning those personal traits and living habits which are related to survival is essential if a rational approach to secondary prevention is to be devised.

The bulk of patients with angina have major obstructions of proximal segments of coronary arteries and a still intact myocardium. In view of this and the serious prognosis of angina in men, a controlled trial to determine the efficacy of prophylactic surgical revascularization in reducing the likelihood of myocardial infarction and in prolonging survival would seem in order.

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Pitfalls in Prediction of Coronary Arterial Obstruction from Patterns of Anterior Infarction on Electrocardiogram and Vectorcardiogram

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Sixty patients with patterns of anterior wall myocardial infarction on electrocardiogram and vectorcardiogram underwent coronary cineangiographic studies. In 47 with patterns of isolated anterior wall infarction, 25 (53 percent) had entirely normal coronary arteries on cineangiogram. Of these, 17 had rheumatic heart disease, 5 primary myocardial disease and 3 no demonstrable abnormality. Only 11 of the 25 (46 percent) had patterns of left ventricular hypertrophy. In the 22 with significant coronary disease on cineangiography, 3 had triple, 12 had double and 7 had single vessel disease. Of 12 patients with combined patterns of anterior and inferior wall myocardial infarction, only 1 (with primary myocardial disease) had normal coronary arteries. Of 12 patients with significant disease, 8 had triple vessel involvement.

Thus, in patients with patterns of anterior myocardial infarction on electrocardiogram and vectorcardiogram who are referred for study primarily because of valvular or myocardial disease, selective coronary arteriography frequently shows complete absence of coronary arterial obstruction. When such patients have coronary artery disease, it is frequently more widespread than anticipated from the electrocardiographic and vectorcardiographic patterns; occasionally, it may spare even the left anterior descending coronary artery. Caution is indicated in the prediction of coronary artery disease from electrocardiographic or vectorcardiographic records, especially in patients selected for catheterization procedures.

Patterns of anterior wall myocardial infarction are frequently observed in patients referred for cardiac catheterization and angiographic procedures for evaluation of coronary, valvular or myocardial problems. The common clinical presumption of coronary artery disease from classic electrocardiographic or vectorcardiographic evidence of patterns of anterior myocardial infarction is often incorrect and may result in serious errors in both diagnosis and treatment of valvular or myocardial heart disease. In other cases when the clinical presumption of coronary disease is confirmed by coronary arteriography, such obstructive disease may be inappropriately localized or surprisingly extensive.[1] The purpose of this study was to determine the predictability of coronary artery disease and severity of vessel involvement from electrocardiographic or vectorcardiographic patterns of anterior wall myocardial infarction.

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TABLE I

Classification of Severity of Coronary Artery Disease

Coronary Artery Disease		Arterial Obstruction
Grade	Severity	(%)
0	Absent	None
1	Mild	0–25
2	Moderate	25–75
3	Severe	75–100

TABLE II

Examples of Grading of Coronary Artery Disease

	Grading of Disease			
Case	RCA	LAD	LCA	
A	0	1	0	No significant disease
B	1	1	1	No significant disease
C	0	2	0	Significant disease
D	3	1	2	Significant disease
E	3	3	3	Significant disease

CAD = coronary artery disease; LAD = left anterior descending artery; LCA = left circumflex artery; RCA = right coronary artery.

TABLE III

Clinical Data in 60 Patients with Patterns of Anterior Infarction

	ECG–VCG Diagnoses of AMI (47 Cases)		ECG–VCG Diagnoses of AMI + IMI (13 Cases)	
	CAD (Grade 2, 3)	No CAD	CAD (Grade 2, 3)	No CAD
no. of cases	22	25	12	1
Male	16	11	7	1
Female	6	14	2	0
Average age (yr)	53	55	52	37
Angina	17	2	10	0
RHD	4	17	2	0
Aortic	3	12	2	0
Mitral	1	5	0	0
IHSS	1	0	...	...
PMD	0	5	0	1
No disease	0	1	...	...
LVH	8	11	6	1

AMI = anterior myocardial infarction; CAD = coronary artery disease; ECG–VCG = electrocardiographic–vectorcardiographic; IHSS = idiopathic hypertrophic subaortic stenosis; IMI = inferior myocardial infarction; LAD = left anterior descending artery; LCA = left circumflex artery; LVH = left ventricular hypertrophy; PMD = primary myocardial disease; RCA = right coronary artery; RHD = rheumatic heart disease.

Material and Methods

Sixty patients were referred for specialized cardiac evaluation. The procedures included a standard 12 lead electrocardiogram, a Frank system vectorcardiogram,[2] right- and left-sided cardiac catheterization as well as coronary arteriography. Vectorcardiograms were displayed using a Hewlett-Packard vector amplifier and visoscope. The loops were photographed with a Polaroid® camera. The oscillopscope had a sensitivity of 1 mv = 5 cm.

Hemodynamic studies were performed after an overnight fast, with patients in the supine position. Right and left heart catheterizations were performed on all patients. The right heart studies were performed using standard Cournand catheters with a platinum tip electrode. The left heart chambers were evaluated by the transseptal technique or retrograde approach through either the femoral artery percutaneously or brachial artery by cut-down procedure. Pressures were recorded on an Electronics for Medicine oscillographic recorder model DR-12 utilizing Statham P23Db strain gauges. The mid-thoracic position was used as the zero pressure reference. Coronary and left ventricular cineangiography was performed in all patients by methods previously described.[3]

Electrocardiographic and Vectorcardiographic Criteria

In all patients studied, anterior QRS forces were absent in the electrocardiogram or vectorcardiogram, or both. The scalar criterion used was absence of R waves in leads V_1 to V_3.[4] The vectorcardiographic criterion was absence of the Q wave in the Frank Z lead.[5] Thus, both the horizontal and right sagittal QRS loops were initially posterior. In 10 patients, the Q wave duration in lead Y exceeded 30 msec, or the QR ratio in lead aVF exceeded 0.25 with a Q duration in aVF of 0.03 second—criteria for inferior wall myocardial infarction.[6]

Left ventricular hypertrophy was diagnosed on the basis of standard scalar criteria: $R_1 + S_3$ greater than 25 mm, or SV_1 or $V_2 + RV_5$ or V_6 exceeding 35 mm.[7] The vectorcardiographic criterion used for left ventricular hypertrophy was a maximal QRS vector exceeding 2.0 mv in any reference plane.[8] Severity of coronary artery disease was classified from the arteriogram as grade 0 for no obstruction, grade 1 for 0 to 25 percent obstruction, grade 2 for 25 to 75 percent obstruction and grade 3 for 75 to 100 percent obstruction (Table I). Combined coronary artery disease was graded in the following manner (Table II): Patients with grade 2 or 3 disease in any artery were considered to have significant coronary artery disease. Those with grade 0 to 1 disease in all arteries were considered free of significant coronary artery disease.

Results

Patients Free of Coronary Disease (Table III)

In 25 of the 60 patients studied, standard criteria for anterior infarction were met, but the disease was grade 1 or less in all 3 coronary arteries on selective coronary arteriography. The clinical data on these patients are shown in Table III.

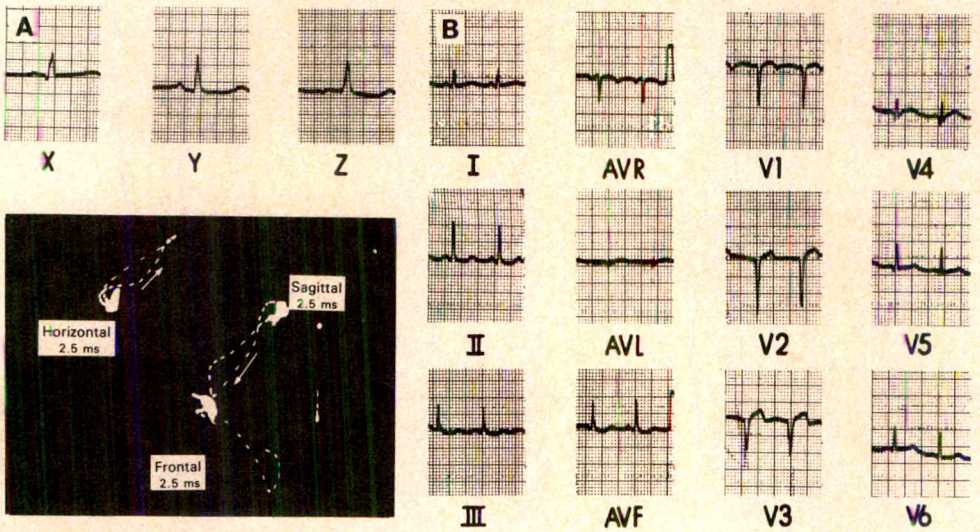

Figure 1. Rheumatic heart disease and aortic stenosis. Normal coronary arteriogram. Anterior infarction pattern in Frank XYZ leads and vectorcardiogram (**A**) and electrocardiogram (**B**).

Rheumatic valvular heart disease was present in 17, primary myocardial disease in 5, atypical angina in 2 and minimal mitral insufficiency in 1. Eleven patients, in addition to patterns of anterior wall myocardial infarction, had high QRS voltage meeting the criteria for the electrocardiographic and vectorcardiographic diagnosis of left ventricular hypertrophy (Table III). One patient met criteria for inferior as well as anterior infarction.

Illustrative Clinical Material

Case 1 (Fig. 1): A 51 year old woman was admitted for evaluation of a basal systolic murmur. The aortic gradient was 40 mm Hg, indicating aortic valvular stenosis. The cardiac index was 2.73 liters/min per m^2. The right and left coronary systems were free of obstruction. The vectorcardiogram and XYZ leads indicated a complete absence of anterior QRS forces. The scalar electrocardiogram showed absence of the R wave in leads V_1 to V_3.

Case 2 (Fig. 2): A 53 year old man was admitted for evaluation of apical systolic and diastolic murmurs. Left heart catheterization studies established the diagnosis of mitral stenosis, with a 22-mm Hg diastolic gradient and grade 3 mitral insufficiency. The cardiac index was 1.97 liters/min per m^2. The coronary arteries were entirely normal. The XYZ leads showed an absence of the Q wave in lead Z. The scalar electrocardiogram indicated absence of the R wave in leads V_1 to V_3.

Case 3 (Fig. 3): A 53 year old woman was evaluated because of apical and basal murmurs. Supraaortic dye injection showed grade 3 aortic insufficiency. A diastolic gradient of 13 mm Hg established the diagnosis of mitral stenosis as well. The cardiac index was 3.55 liters/min per m^2. The coronary arteries were normal. The XYZ leads and vectorcardiographic loops indicate a complete absence of anterior QRS forces consistent with a diagnosis of anterior wall myocardial infarction. The scalar electrocardiogram shows absence of the R wave in leads V_1 to V_3.

Case 4 (Fig. 4): A 38 year old man was studied because of congestive heart failure of obscure origin. No valvular gradients or insufficiency or intracardiac shunts could be demonstrated. Diastolic pressure levels were elevated in all heart chambers, and ventricular contractility was diffusely impaired. The diagnosis was

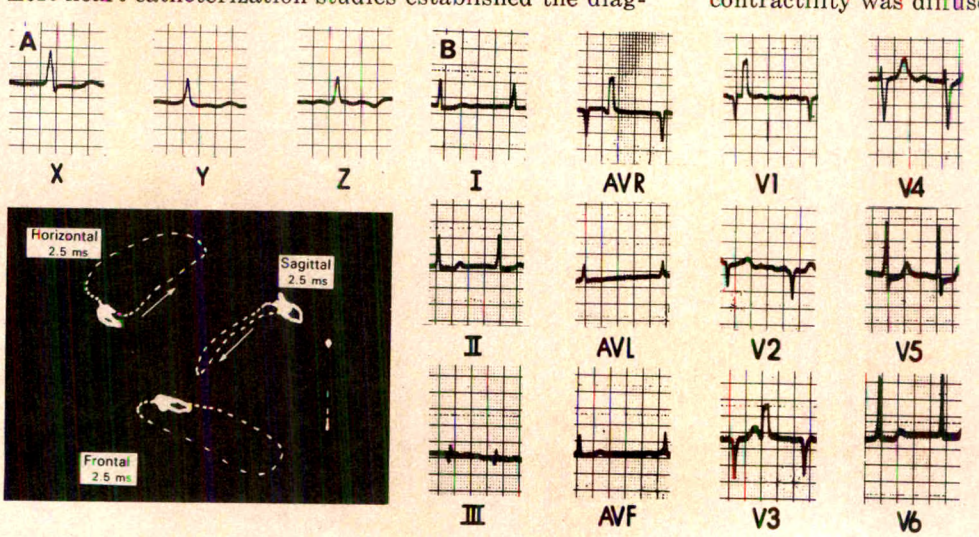

Figure 2. Rheumatic heart disease, mitral stenosis and mitral insufficiency. Normal coronary arteriogram. Anterior infarction pattern in Frank XYZ leads (**A**) and electrocardiogram (**B**).

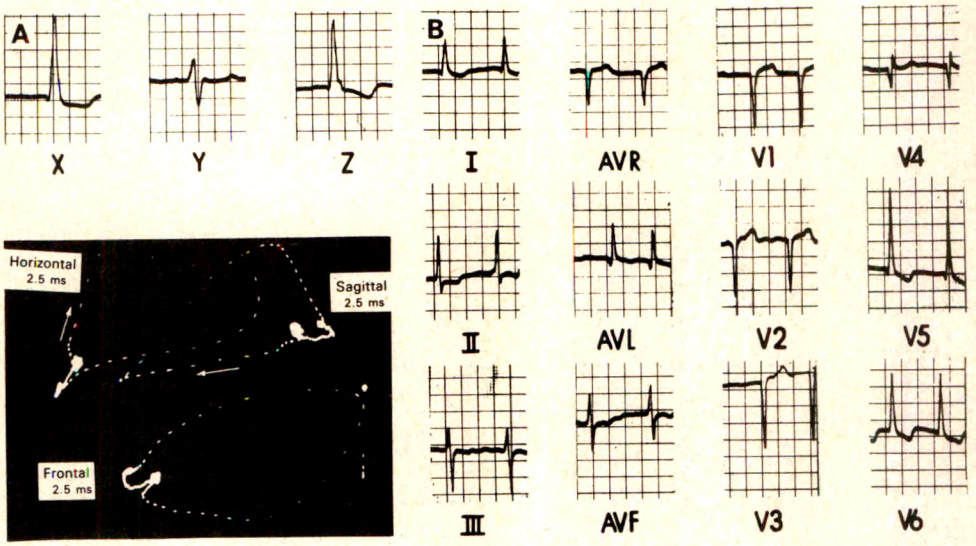

Figure 3. Rheumatic heart disease, aortic insufficiency, mitral stenosis and mitral insufficiency. Normal coronary arteriogram. Anterior infarction pattern in Frank XYZ leads and vectorcardiogram (**A**) and electrocardiogram (**B**).

primary myocardial disease. The coronary arteries were normal on cineangiography. The XYZ leads and vectorcardiograms demonstrated a complete lack of anterior forces. The electrocardiogram corroborated the presence of a pattern of anterior wall myocardial infarction.

Case 5 (Fig. 5): A 35 year old man was admitted for severe congestive heart failure. Catheterization studies and ventriculography showed a high level of diastolic pressure in all chambers, grade 3 mitral regurgitation and markedly impaired ventricular contractility. The diagnosis was primary myocardial disease with mitral insufficiency. The coronary arteries were free of obstructive disease. The XYZ leads and vectorcardiographic loops demonstrated the absence of anterior QRS forces. In addition, the duration of superior QRS forces in lead Y and in frontal QRS loop were of abnormal duration, also consistent with the diagnosis of inferior wall myocardial infarction.

Each of these 5 cases illustrates the unreliability of patterns of anterior wall myocardial infarction in the prediction of coronary artery obstruction. This is particularly true of patients referred for evaluation of valvular disease or obscure congestive heart failure rather than for evaluation of persistent anginal pain.

Patients with Demonstrable Coronary Artery Disease (Tables III and IV)

Coronary artery disease was present on angiography in 22 patients with patterns of isolated anterior infarction on the electrocardiogram and vectorcardiogram (Table IV) and in 12 patients with combined anterior and inferior myocardial infarction. Double vessel disease was the most common finding in the group with isolated anterior infarction (12 of 22 patients). Single vessel disease occurred in 7 patients and triple vessel disease in 3. The left anterior descending artery was the most frequently involved vessel (19 of 22 patients). In 3 patients the anterior descending artery was grade 0 to 1 with major disease in the right and circumflex arteries. Indeed, in 1 patient, the right coro-

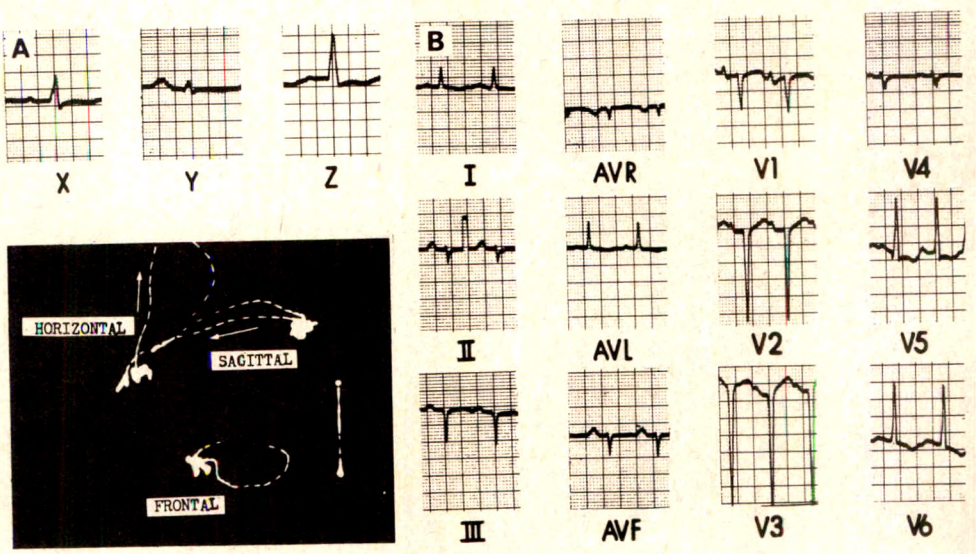

Figure 4. Primary myocardial disease. Normal coronary arteriogram. Anterior wall infarction pattern in Frank XYZ leads and vectorcardiogram (**A**) and electrocardiogram (**B**).

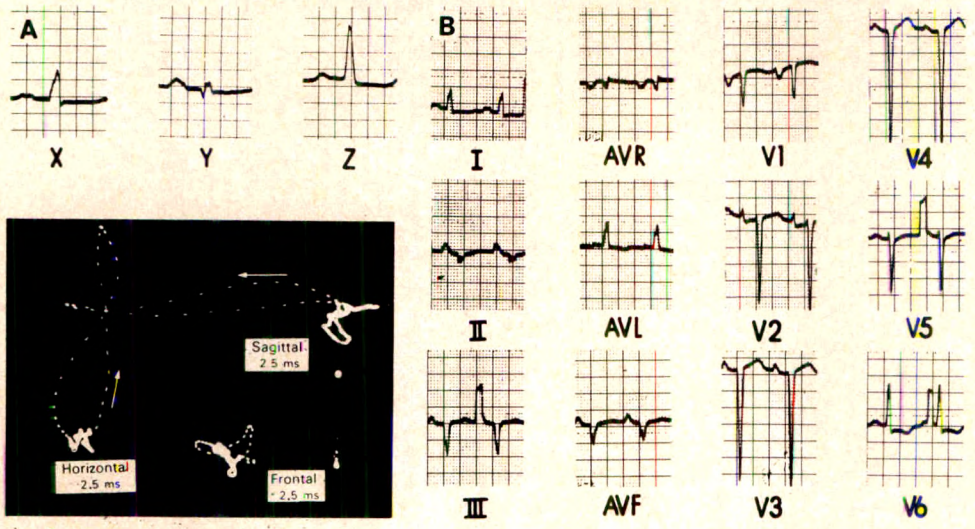

Figure 5. Primary myocardial disease. Normal coronary arteriography. Anterior and inferior infarction pattern in Frank XYZ leads and vectorcardiogram (**A**) and electrocardiogram (**B**).

nary artery was the only diseased vessel. In 14 of 22 patients the right coronary artery was involved, and in 8 the circumflex artery.

Illustrative Case

Case 6 (Fig. 6): A 43 year old man had a clinical anginal syndrome. The electrocardiogram and vectorcardiogram were typical of anterior wall myocardial infarction with absence of anterior QRS forces. Selective coronary arteriography showed minimal disease in the left anterior descending artery (grade 1). However, the right coronary artery was totally obstructed, and the left circumflex artery was 50 percent occluded. Thus, this patient with clinical angina and an electrocardiographic and vectorcardiographic pattern of anterior infarction demonstrated double vessel disease with sparing of the left anterior descending artery.

Of special interest are the 12 patients (Table IV) whose electrocardiographic-vectorcardiographic study met criteria for anterior and inferior wall myocardial infarction. In 8 (67 percent) triple vessel disease was found on selective coronary angiography. The remaining patients had double vessel occlusion. These results confirm the findings of Holt et al.,[9] who encountered multiple vessel obstruction when the electrocardiogram indicated combined anterior and inferior myocardial infarction. Angina was prominent in this overall group of 34 patients with patterns of anterior or anterior plus inferior infarction and coronary artery disease confirmed by coronary angiography. Chest pain was significant in 27 of the 34 patients (Table III). Additional diagnoses were frequently established in this group. Seven patients were found to have physiologic changes of aortic, subaortic or mitral valve disease.

TABLE IV

Distribution and Severity of Lesions in 34 Patients with Patterns of Anterior Wall Infarction and Demonstrable Coronary Artery Disease on Angiography

	AMI (22 Patients)			AMI + IMI (12 Patients)		
Disease	RCA	LAD	LCA	RCA	LAD	LCA
Grade						
3	9	13	3	11	8	6
2	5	6	5	1	3	4
0–1	8	3	14	0	1	2
Vessels involved						
3	3/22	13%		8/12	67%	
2	12/22	55%		4/12	33%	
1	7/22	32%		0	...	

AMI = anterior myocardial infarction; IMI = inferior myocardial infarction; LAD = left anterior descending artery; LCA = left circumflex artery; RCA = right coronary artery.

Discussion

Two common pitfalls await the cardiologist in evaluating an anterior wall myocardial infarction pattern, especially in the patient referred for physiologic and angiographic study. The first is the presumptive diagnosis of coronary artery disease which in fact may not be present. The second is underestimation of the severity of coronary artery disease when it is present.

Pitfall 1—diagnosis of coronary artery disease when coronary arteries are normal: This pitfall occurs primarily among patients with aortic or mitral valve disease or primary myocardial disease. Only about 45 percent of our patients had the increased voltage on electrocardiogram or vectorcardiogram characteristic of left ventricular hypertrophy, in contrast to the findings of Kini et al.[8] However, all of the remaining patients had enlarged hearts by X-ray examination as well as physiologic defects consistent with the development of left ventricular hypertrophy.

Clearly, the balance of early QRS forces may be posterior in the absence of coronary arterial obstruction. Presumably, anterior wall perfusion was

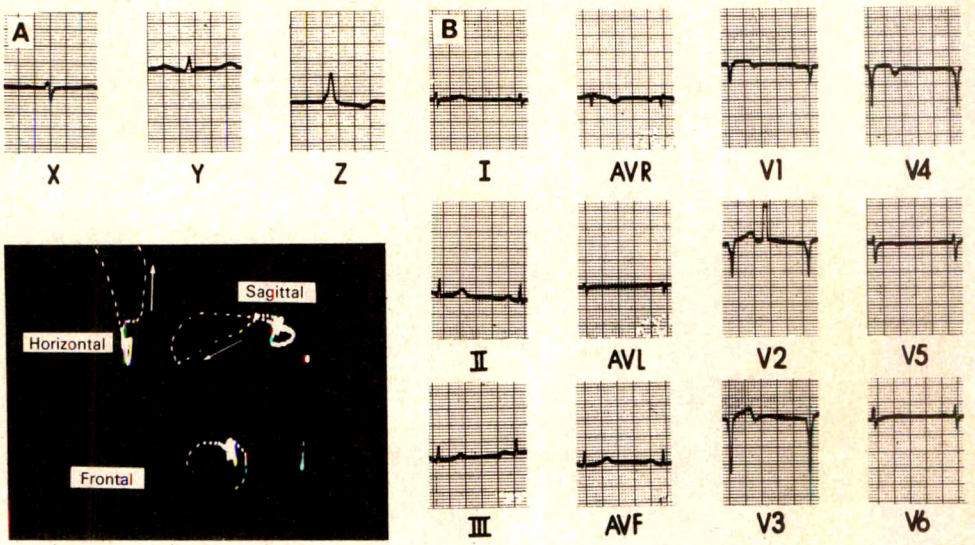

Figure 6. Clinical angina pectoris. Coronary arteriography: right coronary artery totally obstructed; left circumflex artery 50 percent obstructed; left anterior descending artery no significant disease. Anterior infarction pattern in Frank XYZ leads and vectorcardiogram (**A**) and electrocardiogram (**B**).

normal in these patients and, thus, confluent necrosis as seen in ischemic scars was probably not present. Several mechanisms might account for the findings in this group. Myocardial fibrosis involving the septum and anterior surface of the left ventricle might well result in the loss of anterior wall forces, especially in combination with left ventricular hypertrophy.[7,10–12] Commonly, in advanced left ventricular hypertrophy with high QRS voltage, and especially with ST–T segment changes, the anterior QRS forces are markedly reduced or absent. Our observations suggest that left ventricular hypertrophy, although evident by X-ray study but not by high QRS voltage, may be associated with absence of anterior forces and subsequent anterior wall myocardial infarction pattern. Ventricular dilatation and diffuse myocardial degeneration, as commonly encountered in primary myocardial disease,[3] may well result in a leftward shift of the early QRS forces.[13,14]

Three patients in our series with patterns of anterior infarction were found to have no evidence of valvular, myocardial or coronary disease. Welch et al.[15] demonstrated evidence of myocardial infarction electrocardiographically in 109 patients; 6 had entirely normal coronary arteries cineangiographically. Two patients had primary myocardial disease. Two patients did not have definite evidence of myocardial infarction on reexamination of the electrocardiogram. One patient had blunt trauma to the chest and 1 may have had myocarditis; 1 case remains unexplained. Campeau et al.[16] found no obstructive coronary disease on cineangiographic examination in 6 of 350 patients with clinical myocardial infarction. They suggested that infarction may be caused by arterial occlusion not evident on coronary arteriography or that the "infarction" was not caused by occlusion. The former possibility was believed to be due to overlooked occlusion,[1] disease of the microcirculation,[17] temporary occlusion by a functional constriction (spasm) or lysis of thrombus or emboli (recanalization). "Infarction" not caused by a coronary arterial occlusion may be due to a decrease in coronary blood flow,[18] impairment of oxygen diffusion or utilization, or both,[19] coronary arteriovenous shunting or nonischemic necrosis. Great caution must therefore be exercised in predicting coronary arterial obstruction from patterns of anterior wall myocardial infarction, especially in the absence of anginal pain or in the presence of valvular or primary myocardial disease.

Pitfall 2—underestimation of severity of coronary disease: When the coronary arteriogram confirms the diagnosis of arterial obstruction, double or even triple vessel disease is commonly encountered. As described by Gunnar,[10,11] Holt,[9] and Lee[20] and their co-workers, the observed disease is more extensive than might be predicted from the electrocardiographic and vectorcardiographic findings alone. These observations confirm the older findings of Blumgart et al.[21] on the frequency of multiple coronary arterial obstruction in autopsy specimens studied by injection techniques. A similar recent study on a large series of autopsy cases reported a high incidence of double and triple vessel disease.[22]

In 1,184 autopsy cases studied by Horan et al.,[23] 118 subjects had patterns of isolated anterior or anteroseptal infarction; 49 had no evidence of myocardial scarring; and 69 had myocardial scars suggesting myocardial infarction. All 15 patients in the series of 1,184 with patterns of combined anterior and inferior infarction had myocardial scars. The coronary arteries were not described. When the criteria for anterior and inferior infarction are met, the most common coronary involvement encountered is triple vessel disease. Nevertheless, the combined patterns of anterior and inferior infarction may occasionally be encountered in a patient entirely free of coronary artery disease (Fig. 5).

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Clinically Suspect Ischemic Heart Disease Not Corroborated by Demonstrable Coronary Artery Disease

Physiologic Investigations and Clinical Course

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In 11 patients with angina pectoris and abnormal stress electrocardiograms, no narrowing or obstruction of coronary vessels was visible by selective cut film and coronary cinearteriography. One patient showed chemical evidence of myocardial hypoxia despite normal arteriograms. Similar evidence of impaired myocardial oxygen supply was absent in the remaining 10 patients. We found no abnormality in hemoglobin O_2 affinity which might jeopardize myocardial O_2 supply. The clinical course of these patients, including that during a 1 to 2 year followup period, has not been complicated by myocardial infarction or cardiac failure. In 5 symptoms have decreased.

In the vast majority of patients who have chest pain and electrocardiographic abnormalities characteristic of ischemic coronary heart disease, narrowing or obstruction of major coronary arteries can be demonstrated by coronary arteriography.[1–4] However, in some patients with indistinguishable clinical findings, the coronary arteriograms are normal.[5–8] Chemical evidence of myocardial hypoxia has been reported to occur in these patients despite normal coronary arteriograms,[6,7] and abnormal hemoglobin oxygen affinity has been proposed as a basis of the myocardial hypoxia.[9]

We studied 11 patients who had episodic chest pain resembling angina pectoris which was substantiated by electrocardiographic abnormalities of myocardial ischemia, but who had no coronary artery disease demonstrable by arteriography. We found the following: (1) Chemical evidence of myocardial hypoxia in these patients was rare compared to that in patients with demonstrable coronary atherosclerosis; (2) the equilibrium O_2 dissociation curves of these patients did not differ from those of normal subjects; and (3) over a subsequent 1 to 2 year period some showed a decrease in symptoms and none experienced clinically evident myocardial infarction.

Methods

Patients: The criteria for selection of patients were (1) periodic chest pain clinically similar to angina pectoris, (2) positive responses to stress electrocardiography, and (3) no coronary artery disease demonstrable by coronary arteriography. No patient was taking digitalis or other cardiac medications at the time of electrocardiographic or coronary venous catheterization study. Patient 5 had taken digitalis, 100 mg, and hydrochlorthiazide, 50 mg, daily; administration of these drugs had been discontinued 1 month before the study.

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TABLE I

Clinical and Electrocardiographic Data

Case no.	Sex & Age (yr)	Chest Pain		Conditions Precipitating Pain					Effect of NTG	Family History*	Stress ECG	
		Present (yr)	Duration (min)	Exertion	Emotion	Night	Meals	Cold			Hypoxemia	Exercise
1	M33	2	5–30	+	+	+	0	0	+	+	+	+
2	F54	7	5–10	+	0	0	0	0	+	0	+	+
3	F48	2	5–10	+	+	+	0	0	+	0	+	+
4	F58	7	5–60	+	+	0	0	+	0	0	+	+
5	F57	1¼	15–120	+	0	0	0	0	†	0	+	+
6	F57	5	5–60	+	0	0	0	0	0	0	+	0
7	F45	½	5–10	+	+	+	0	0	0	+	0	+
8	F59	3	30	+	0	0	0	0	+	0	+	+
9	M43	10	60	0	+	+	0	0	†	0	+	0
10	F48	7	1	+	0	0	0	0	0	0	+	0
11	F55	1½	5	+	+	0	0	0	+	0	+	+

* Parent, grandparent, sibling, aunt or uncle with probable coronary disease before age 60 years.
† Nitroglycerin never used.
NTG = nitroglycerin.

Investigative procedures: Standardized stress electrocardiography was performed with hypoxemia and graded exercise. The patients pedaled a bicycle ergometer for 4 minute periods at increased levels of work load, separated by rest intervals. For the hypoxemia test, the patients breathed 10 percent O_2 in nitrogen for 20 minutes. Exercise and hypoxemia were continued until the patients experienced chest pain, significant S–T segment depression, or exhaustion, or had a heart rate of 85 percent of the maximal value predicted according to age.[10] Segmental S–T depression of 0.5 mm or greater for the hypoxemia test and 1.0 mm or greater for the exercise test was considered a positive result.[10] Left ventricular pressures were obtained with the patient supine, and left ventricular cineangiograms were filmed in the right anterior oblique projection. Selective coronary arteriography was performed with injections directly into the right and left coronary artery orifices. Films were taken in the left lateral, 70° left anterior oblique and 15° right anterior oblique positions using both high definition rapid serial large-cut film, and conventional cine techniques.[11]

For study of myocardial O_2 supply, coronary venous blood samples were obtained from a catheter positioned in the coronary sinus. We made observations initially with the patients at rest (control) and then while their myocardial O_2 requirement was increased by electrical pacing of the right atrium at a rate of approximately 120/min. Pacing was unsuccessful in Patients 7 and 10, and their heart rate was increased to 86/min and 97/min, respectively, by intravenous administration of 1.0 mg of atropine. The methods for determining blood lactate and pyruvate concentrations have been described.[12] Blood O_2 concentration was determined by the manometric method in Patients 1 to 6, but was calculated from the blood pO_2 and pH (Radiometer Co., Copenhagen), hemoglobin concentration (spectrophotometric) and blood O_2 dissociation curve in Patients 7 to 11. The development of myocardial hypoxia during the tachycardia was judged by a greater than 10 percent increase in the lactate:pyruvate concentration ratio in the coronary venous blood (L/P_{cv}).[12]

Blood oxygen affinity was determined from the O_2 dissociation curve of whole blood and is expressed as the pO_2 at which the hemoglobin is 50 percent saturated with O_2 (P_{50}).[13] In 1 patient, hemoglobin electrophoresis was carried out at pH 7.0 and 8.6 by the method of Huisman.[14]

Results

Clinical features of the patients (Table I): Nine of the patients were women, and the mean age was 51 years. Chest pain occurred especially during physical exertion or emotional disturbance and frequently woke the patient at night. The duration of the pain, which often exceeded 10 minutes in 6 patients, was longer than that typically reported for patients with coronary heart disease.[15] Five patients stated that sublingually administered nitroglycerine shortened the duration of pain. None had evidence of a previous myocardial infarction, and only 2 presented a family history of coronary heart disease. No consistent behavioral pattern characterized this group of patients, nor did they exhibit an unusual number of physical complaints. Patient 8 had a heart murmur probably due to a small patent ductus arteriosus, and Patient 11 had a slightly increased systemic arterial blood pressure. In no instance was an extracardiac explanation for chest pain apparent. All had normal cardiac silhouette and lung fields on their chest roentgenogram. Left ventriculograms showed normal ventricular size and contractility. Left ventricular end-diastolic pressures ranged from 5 to 11 mm Hg.

The resting electrocardiogram was normal in all except Patient 5, who had S–T segment depression in leads II, III and V_4 to V_6. The results of the hypoxemia and exercise stress tests are shown in

Table I. In all patients, significant S–T segment depression occurred during 1 or both stress tests.

Myocardial oxygen studies (Table II): The control coronary arteriovenous (a–v) differences for blood O_2, lactate and pyruvate concentrations were comparable to those found in normal subjects.[12] The changes in coronary venous blood lactate: pyruvate concentration (L/P_{cv}) and coronary blood (a–v)O_2 difference during tachycardia are presented in Figure 1, where they are compared with similar data previously reported for 6 normal subjects.[12] In the normal subjects, heart rate was increased to values ranging from 87 to 124/min (mean 107); in the present patients, to values ranging from 86 to 129/min (mean 113). In 1 patient (Case 3) increase in heart rate by electrical pacing caused a reversal of the coronary (a–v) difference in blood lactate concentration from a positive to a negative value (lactate uptake reversed to lactate output by the myocardium) as well as a significant increase in L/P_{cv}. This patient had no accompanying change in coronary blood (a–v)O_2 difference or coronary venous blood pO_2 and did not experience chest pain during the tachycardia. In all of the other 10 patients, the L/P_{cv} and coronary blood (a–v)O_2 remained constant or decreased during tachycardia, as previously observed in the normal subjects. None experienced chest pain. The tachycardia caused no significant change in arterial blood pO_2 (mean control 78.2 mm Hg, mean tachycardia 77.1 mm Hg). Changes in systemic arterial blood pressure were comparable to those found in normal subjects.[12]

Blood O_2 affinity was determined in 10 patients (all but Case 1), and the P_{50} values (pO_2 at 50 per cent O_2 saturation) are presented in Figure 2 right panel. The mean P_{50} (27.3 mm Hg) was virtually the same as that of normal subjects (Fig. 2 left panel), although in 2 (Cases 4 and 7) the P_{50} value was less than that observed in any subject in the normal group (higher O_2 affinity). Electrophoresis of the hemoglobin was performed in the patient with the lowest P_{50} value, and was normal.

Coronary arteriography: No significant narrowing or obstruction of the coronary arteries or development of collateral circulation could be seen

TABLE II

Myocardial Oxygen Supply

Case no.	Condition	Heart Rate (beats/min)	Arterial Blood Pressure (mm Hg)	O_2 Concentration (ml/100 ml)		Cor. Venous		Lactate (mM)		Pyruvate (mM)		Lactate: Pyruvate Ratio	
				Art.	Cor.(a–v)	pO_2	pH	Art.	Cor.(a–v)	Art.	Cor.(a–v)	Art.	Cor. Ven.
1	C	78	111/52	18.2	10.2	...	...	0.37	0.12	0.068	0.024	5.5	5.8
	H	113	104/59	18.0	10.3	...	...	0.41	0.13	0.074	0.026	5.6	5.8
2	C	74	148/76	17.5	11.3	...	...	0.49	0.14	0.084	0.029	5.8	6.3
	H	110	151/87	17.4	11.4	...	...	0.49	0.18	0.087	0.029	5.7	5.4
3	C	74	149/79	15.1	10.3	20.5	7.37	0.38	0.09	0.066	0.014	5.7	5.6
	H	129	143/92	15.5	10.6	19.9	7.35	0.39	—0.07	0.067	0.011	5.8	8.2
4	C	64	138/72	15.1	9.8	...	7.37	0.43	0.10	0.073	0.017	5.9	5.9
	H	111	140/89	15.2	9.8	...	7.39	0.48	0.11	0.070	0.007	6.8	6.1
5	C	72	153/87	16.6	12.1	...	7.38	0.34	0.13	0.069	0.027	4.9	5.0
	H	113	145/95	16.6	11.8	...	7.37	0.33	0.14	0.065	0.020	5.0	4.2
6	C	86	152/85	15.2	11.4	...	7.32	0.34	0.10	0.068	0.013	5.0	4.4
	H	122	154/95	15.6	11.4	...	7.31	0.35	0.07	0.070	0.011	4.9	4.6
7	C	60	152/88	14.6	10.4	17.8	7.36	0.34	0.06	0.074	0.018	4.5	5.0
	H	86	152/93	14.7	10.0	19.2	7.35	0.32	0.05	0.068	0.015	4.7	5.0
8	C	71	115/51	16.0	11.2	21.0	7.36	0.38	0.24	0.078	0.031	4.9	3.0
	H	119	99/50	16.0	11.0	21.0	7.39	0.35	0.21	0.075	0.025	4.7	2.9
9	C	83	110/71	18.3	13.5	19.1	7.36	0.40	0.06	0.071	0.005	5.6	5.2
	H	119	111/69	18.2	13.4	19.3	7.36	0.34	0.07	0.068	0.004	5.0	4.3
10	C	62	124/74	17.4	12.1	17.7	7.40	0.43	0.12	0.079	0.026	5.4	5.9
	H	97	122/85	17.0	11.1	19.2	7.41	0.38	0.11	0.074	0.020	5.2	5.1
11	C	85	161/94	16.7	13.0	18.3	7.37	0.88	0.42	0.165	0.085	5.3	5.7
	H	122	156/104	17.0	13.1	18.6	7.38	0.92	0.47	0.154	0.074	6.0	5.7
Mean*	C	74	136/75	16.6	11.5	18.7	7.37	0.44	0.15	0.083	0.028	5.3	5.2
SD		10	20/15	1.2	1.2	1.4	.02	0.16	0.11	0.029	0.022	0.4	0.9
	H	111	133/83	16.6	11.3	19.5	7.37	0.44	0.15	0.081	0.023	5.4	4.9
		12	22/17	1.2	1.2	0.9	.03	0.18	0.12	0.027	0.020	0.6	0.9

* Mean and standard deviation values excluding Patient 3 (who showed evidence of myocardial hypoxia).

In some instances values represent a single set of observations, and in others they represent the means of 2 to 4 sets.

Art. = arterial; a-v = arteriovenous; C = control; cor = coronary; H = heart rate increased by electric pacing or atropine; Ven. = venous.

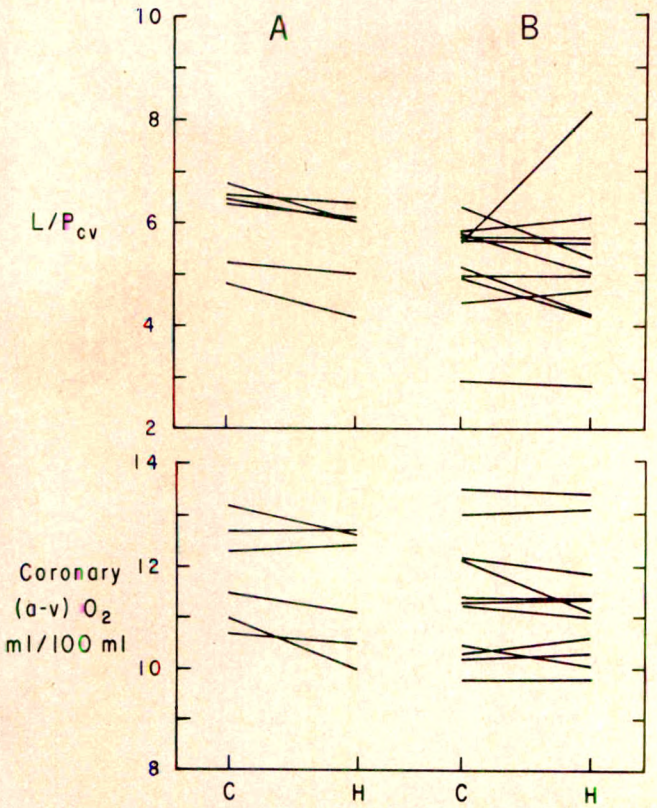

Figure 1. The effect of tachycardia on the coronary venous blood lactate: pyruvate concentration ratio (L/P_{cv}) and the coronary blood $(a-v)O_2$ in normal subjects (**A**) and present patients (**B**). Each line represents a single subject and joins his control value (**C**) with his value during increased heart rate (H). The present patients are compared with normal subjects without heart disease reported previously.[12] (There is a systematic error in the pyruvate and L/P data in reference 12: the pyruvate values published there should be multiplied by 0.607. The L/P values for the normal subjects have been corrected here.)

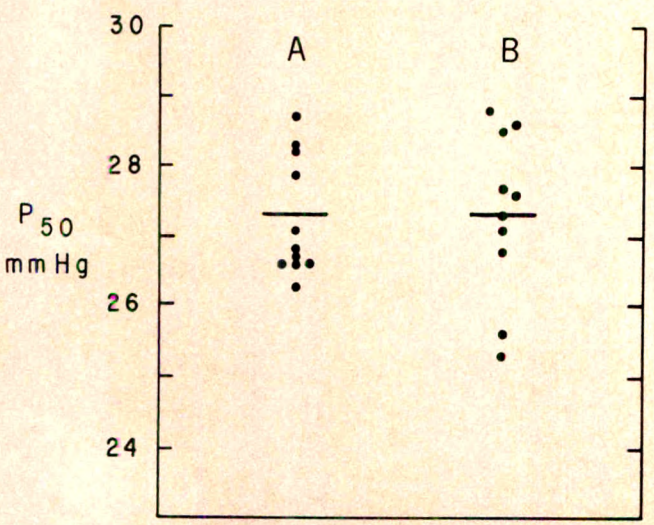

Figure 2. The hemoglobin O_2 affinity, expressed as the pO_2 at which the hemoglobin is 50 percent saturated with O_2 (P_{50}). The present patients (**B**) are compared with normal subjects (**A**) described previously.[13] Each dot represents a single subject. The horizontal lines represent the means of the 2 groups.

TABLE III

Followup Study

Case no.	Length of Followup (mo.)	Chest Pain Still Occurs	Pain Frequency		
			Increased	Decreased	Unchanged
1	*	...	...	...	...
2	28	+	+	...	...
3	28	+	...	+	...
4	27	+	...	...	+
5	26	+	...	+	...
6	25	+	...	...	+
7	24	+	...	...	+
8	16	0	...	...	...
9	14	+	...	+	...
10	14	0	...	...	...
11	13	+	...	...	+

* No followup data in Case 1.

on the coronary arteriograms. Some other patients were excluded from this report on the basis of minor coronary disease which was apparent only on the high definition large-cut films and which probably would have been overlooked on the cineangiograms alone. We were unable to find any pattern of distribution or size of the coronary arteries that was unusually prevalent in these patients. A small, and probably insignificant, arteriovenous fistula from the anterior descending branch of the left coronary artery to the pulmonary artery was present in Patient 5.

Followup study: One year after the last patient was studied, we sent a followup questionnaire to each patient, which was returned to us by all but Patient 1, whom we could not locate. The followup period ranged from 13 to 28 months in different patients (Table III). Episodic chest pain disappeared in 2 patients and decreased in frequency in 3 others; it became more frequent in only 1. No patient experienced symptoms suggesting myocardial infarction during the followup period.

Illustrative Case Reports

The clinical features of 2 of these patients are more completely described in the following reports; those of a third have already been reported in detail.[7]

Case 2: This patient was a 54 year old housewife who had experienced bouts of chest pain for 7 years. Recent increase in frequency of the pain prompted her physician to refer her to the Medical School Hospital. The pain, dull and aching, arose behind her left breast, often extending to the medial aspect of her left upper arm. The onset of pain invariably occurred when the patient was physically active—walking hurriedly, hanging clothes or lifting. Then, upon cessation of the activity, the pain subsided within 5 minutes. Taking nitroglycerin sublingually would shorten the period to 2 minutes. In spite of the consistent relation of her symp-

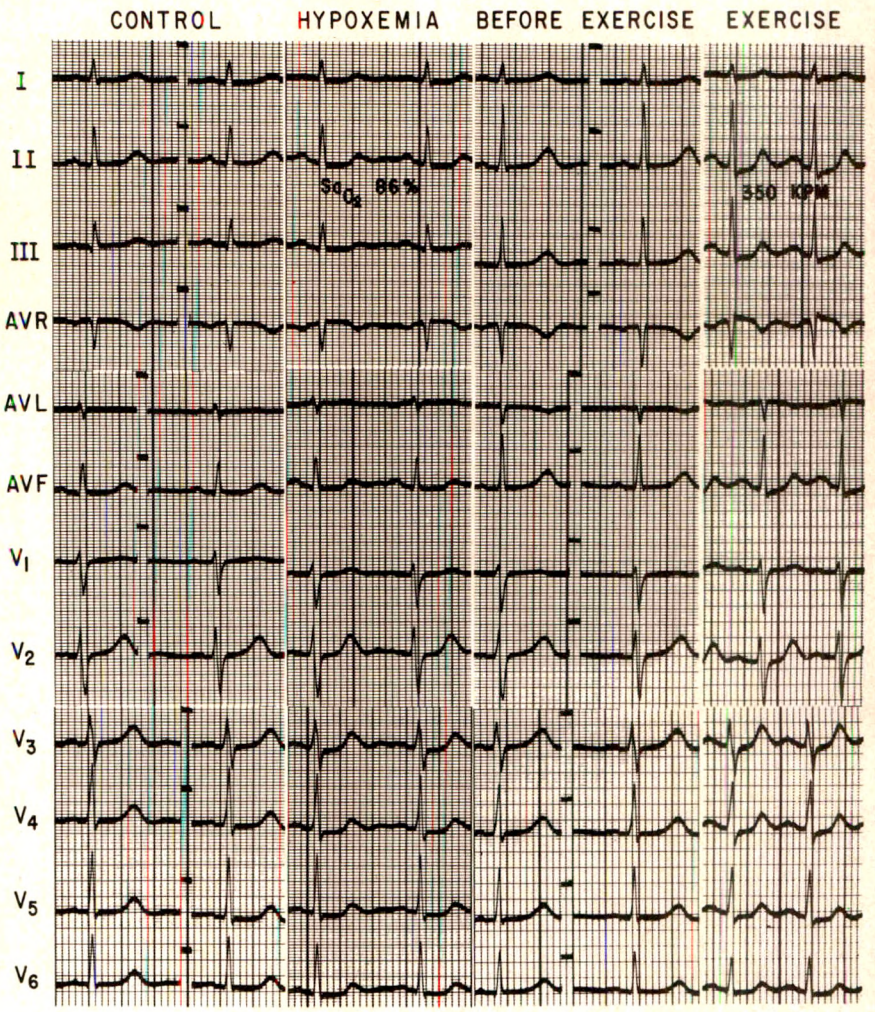

Figure 3. Case 2. Stress electrocardiogram. The resting control tracing (**left panel**) is normal. After breathing 10 percent O_2 for 5 minutes, arterial blood O_2 saturation (SaO_2, determined by ear piece oximeter) decreased from 96 to 86 percent, and segmental S–T depression occurred in leads II, III, aVF and V_4 to V_6, indicating myocardial ischemia. There was no chest pain. The electrocardiographic leads were moved from the legs to the costal margins before exercise. Then, the subject pedaled a bicycle ergometer with graded loads to 350 kpm, causing pain in the medial aspect of the left arm, predominantly junctional S–T segment depression in leads II, III and aVF, and segmental (ischemic) S–T depression in leads V_4 to V_6.

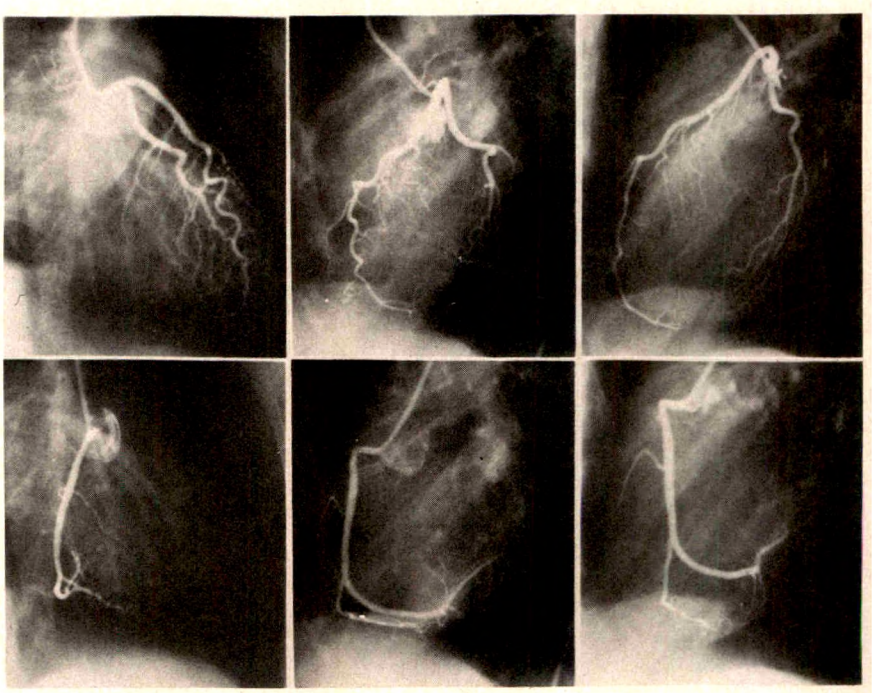

Figure 4. Case 2. Selected cut films of coronary angiograms. **Top panels** show left coronary arterial injections in (from left to right) right anterior oblique, left anterior oblique and left lateral positions. **Bottom panels** show right coronary arterial injections in the same 3 positions.

toms to exertion, on other occasions she could accomplish the same exertion, or more, without the slightest difficulty.

Aside from mild intermittent constipation, the patient had had no other significant illness. Menopause occurred spontaneously at age 49 years. Medications were aspirin, milk of magnesia and nitroglycerin; she took no tobacco and little alcohol. There was no known family history of heart disease, and both parents lived into their ninth decade.

Physical examination disclosed the following: height 166 cm, weight 64 kg, pulse 72/min, blood pressure 120/76 mm Hg, respirations 14/min, temperature 36.9C. She was slightly obese with a calm, easy-going outward appearance. There were varicose veins in both legs but no edema. There were no abnormal findings on cardiac examination. Laboratory findings were as follows: routine hematologic examination normal; urinalysis 3 to 5 white cells per high powered field; blood urea nitrogen 18, creatinine 0.9, fasting blood sugar 80 and total cholesterol 160 mg/100 ml. Chest roentgenogram was normal. Resting electrocardiogram was normal, but exercise as well as hypoxemia caused clearly abnormal S–T segment depression (Fig. 3). Left ventricular cineangiography showed normal ventricular size and contractility. Left ventricular end-diastolic pressure was 9 mm Hg. Selective left and right coronary arteriography showed normal findings (Fig. 4).

Exertional chest pain continued to occur with gradually increasing frequency during the 28 months in which she was home as a housewife after her cardiovascular investigation.

Case 7: This patient, a 45 year old nurse, experienced progressively severe episodic chest pain for 6 months. Her pain, at times substernal tightness and at others a substernal crushing sensation radiating to the throat, jaw, left shoulder or left scapular region, was precipitated by walking uphill or climbing stairs, but more often by emotional excitement. When intense, the pain was accompanied by perspiration and nausea. Initially, she attempted to ignore the pain and to persist in her exertion. However, this approach was never successful and only intensified the pain, at length forcing her to rest, which brought relief within 5 minutes. Relief was not further hastened by administration of nitroglycerin. As her pain became more frequent, it began to occur at night and woke her from sleep.

For the past 2 years she has noted occasional periods of fatigue, lightheadedness and muscle weakness occurring in the late afternoon and disappearing after eating. A total hysterectomy was performed for bleeding myomas at age 43 years. Medications were aspirin, Darvon® and Librium®. She has smoked 1 pack of cigarettes daily for 30 years. Use of alcohol is slight. Her father died from a heart attack at age 48 years.

Physical examination showed height 170 cm, weight 59 kg, pulse 80/min, blood pressure 110/65 mm Hg, respirations 16/min, temperature 37.0C. Her appearance was tense and anxious, and her hands cool and moist. Tenderness in the left anterior fourth intercostal space was discovered on 1 occasion, but did not persist. There were no abnormal findings on cardiac examination. Laboratory findings were: hematocrit 37 vol %, hemoglobin 11.3 g/100 ml, white blood cell count

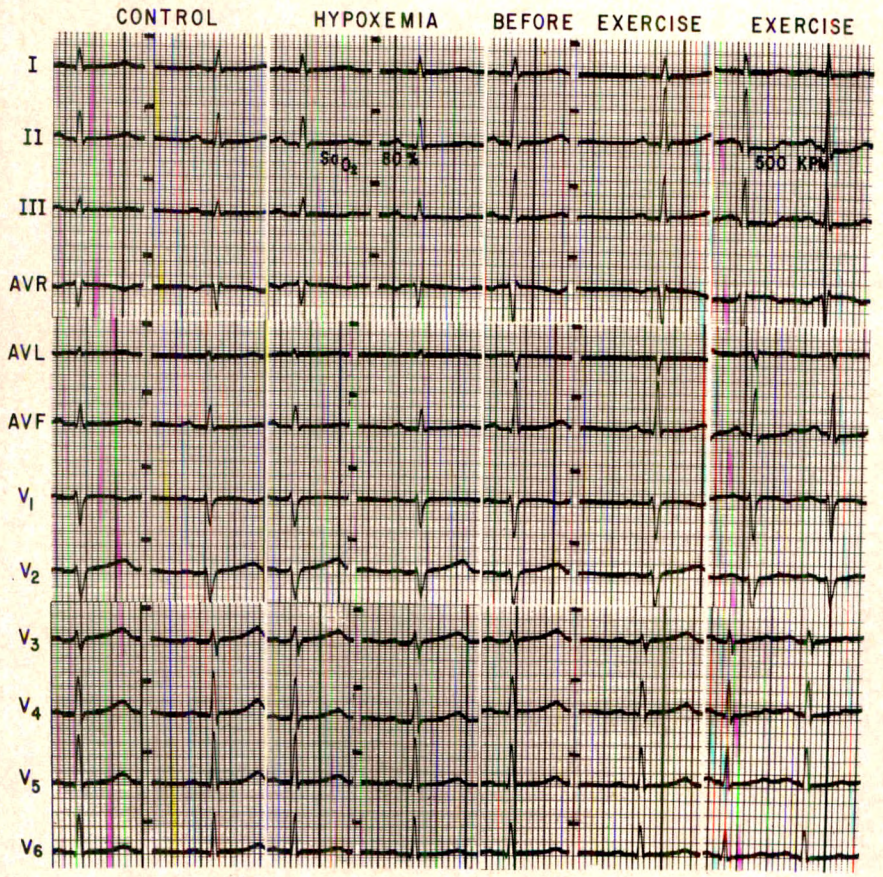

Figure 5. Case 7. Stress electrocardiogram. The resting control tracing (**left panel**) is normal. After breathing 10 percent O_2 for 15 minutes, SaO_2 decreased from 95 to 80 percent, the subject felt lower substernal and right shoulder pain, but no significant electrocardiographic changes occurred. With the electrocardiographic leads moved to the costal margins, the subject pedaled a bicycle ergometer with graded loads to 500 kpm, causing substernal pain, and segmental S–T depression in leads II and III compatible with myocardial ischemia.

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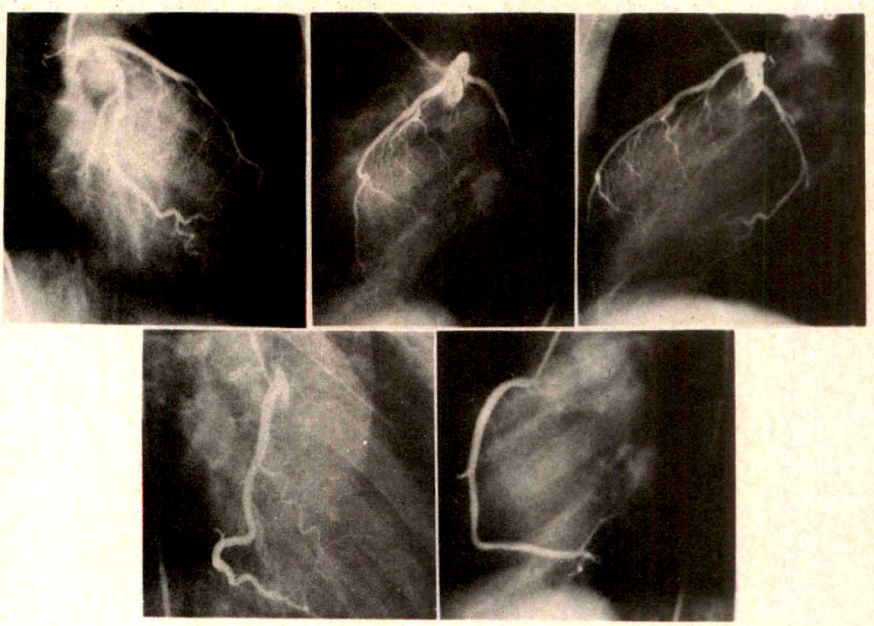

Figure 6. Case 7. Selected cut films of coronary angiograms. **Top panels** show left coronary arterial injections in (from left to right) right anterior oblique, left anterior oblique and left lateral positions. **Bottom panels** show right coronary arterial injections in this patient taken only in the right anterior oblique (**left panel**) and left anterior oblique (**right panel**) positions.

and differential normal; urinalysis 6 to 8 red cells per high power field; urine culture no growth. Lupus erythematosus preparation, direct Coombs test, rheumatoid factor, serum protein electrophoresis were normal. Blood urea nitrogen was 9 and total cholesterol 216 mg/100 ml; fasting blood sugar was 80 mg/100 ml and glucose tolerance tests on 2 occasions demonstrated functional hypoglycemia, blood glucose decreasing to 42 and 45 mg/100 ml at 3 hours. X-ray examination of chest, cervical and thoracic spine was normal. Electrocardiogram was normal at rest, but S–T segment depression just beyond normal limits occurred during exercise (Fig. 5). Left ventricular cineangiography showed normal ventricular size and contractility. Left ventricular end-diastolic pressure was 9 mm Hg. Selective left and right coronary arteriography showed normal findings (Fig. 6). Hemodynamic data from right heart catheterization were normal. Resting mean pressures were right atrium 3, pulmonary artery 11 and pulmonary "capillary wedge" 6 mm Hg; cardiac index was 4.7 liters/min per m^2, and mixed venous blood O_2 saturation was 76 percent.

We have observed this patient for 2 years following her investigation. Thorough examination for an orthopedic origin of her chest pain has had negative results. Her symptoms are unchanged but do not prevent her from working.

Discussion

Chemical evidence of myocardial hypoxia during stress: In patients in whom obstructive coronary disease is demonstrated by arteriography, myocardial hypoxia due to a limited capacity to increase coronary blood flow through the narrowed vessels provides a plausible pathophysiologic explanation for chest pain and electrocardiographic abnormalities when myocardial O_2 needs suddenly increase, as on physical exertion. However, in patients whose coronary arteries appear normal on arteriographic examination, the pathophysiology of similar clinical manifestations is mysterious. A crucial question, which we attempted to answer in our study, is whether the chest pain and electrocardiographic abnormalities in patients without demonstrable coronary atherosclerosis also signify the presence of underlying myocardial hypoxia produced by some alternative mechanism that interferes with myocardial O_2 supply. Such a mechanism might be microscopic coronary vessel disease, failure of coronary vasodilation, abnormal affinity of hemoglobin for O_2, or myocardial metabolic defect. In the majority of patients who do have documented coronary atherosclerosis, myocardial hypoxia can be detected by a chemical change in the coronary venous blood draining the myocardium, that is, increased coronary venous lactate:pyruvate ratio (L/P_{cv}), when the heart rate is increased even to only modestly high levels by electrical pacing or administration of atropine.[12] Moreover, angina pectoris occurs during this type of tachycardia in about half of the patients with coronary disease. Yet, none of the patients in our study experienced chest pain, and only 1 showed chemical signs of myocardial hypoxia when the heart rate was increased to equivalent levels by the same method. Thus, when myocardial O_2 needs are increased by induced tachycardia, myocardial hypoxia and chest pain that occur in patients with coronary disease were absent in the study group. We interpret this finding to mean that the symptoms in our patients were not due to limited coronary reserve leading to myocardial hypoxia during stress, as is the case in coronary heart disease, but had a different basis.

We recognize 2 weaknesses in this line of reasoning which render our conclusion tentative and acceptable only until further evidence emerges. The first of these pertains to the degree, and the

second to the type of stress employed. Although the same degree of tachycardia that we used produced chemical signs of myocardial hypoxia in the patients with coronary disease previously described, a still higher heart rate stress might be required to elicit the hypoxia in the present patients if they had a coronary disorder of lesser magnitude or different nature. Secondly, it could be pertinent that the chest pain occurring under natural conditions in the present patients is brought on by physical exertion or emotion, not by electric pacing. In contrast to our experience in patients with coronary atherosclerosis, the type of stimulus might be critical in a different type of coronary disorder. Another group of investigators reported a high incidence of myocardial hypoxia during administration of isoproterenol in patients with episodic chest pain and normal coronary arteriograms.[6] Whether this difference from our results represents an underlying difference in the coronary response of these patients to electrical pacing as opposed to their response to physical exertion or isoproterenol is a possibility that needs to be investigated. The opposing results of the 2 investigations could be due also to the difference in radiologic techniques used to exclude coronary atherosclerosis.

The single case in which the patient did show chemical signs of myocardial hypoxia may represent a different entity from the other 10. This patient was the subject of a previous communication.[7] The mechanism of her hypoxia is unknown, although some theoretical possibilities have been proposed.[7]

Hemoglobin O_2 affinity: We investigated the suggestion previously made[9] that a failure of the hemoglobin to release its O_2 normally might be responsible for myocardial hypoxia in the absence of coronary artery disease or ischemia. One possibility is that an increased affinity of hemoglobin for O_2 might shift the equilibrium O_2 dissociation curve. This condition would have been detected by a low pO_2 and high O_2 concentration in samples of coronary venous blood, as well as by a low P_{50}, neither of which was found in these patients. Another possibility is that the difficulty in removing O_2 from the hemoglobin might be due solely to a slow rate of release, too slow to permit equilibration during the brief passage of blood through the capillaries. In this case, the pO_2 might be low in the capillaries (if O_2 diffusion into the myocardium exceeded its rate of release by the hemoglobin), but would rise subsequently as more O_2 dissociated, and the coronary venous blood pO_2 might be normal or above normal by the time we determined it in the laboratory. However, there is a common denominator for either possibility: If the O_2 were not released by the hemoglobin, it would remain in the blood, resulting in high coronary venous blood O_2 concentration. But, coronary venous blood O_2 concentration and coronary blood $(a–v)O_2$ in these patients were the same as in normal subjects. Not only does the normal mean P_{50} value in this group of patients demonstrate normal blood O_2 affinity at equilibrium, but their normal mean coronary blood $(a–v)O_2$ difference is strong independent evidence against a significant defect of any type in the release of O_2 by hemoglobin in their coronary capillaries.

Clinical implications: The characteristics of the chest pain as a symptom were comparable to those of patients with coronary heart disease. However, 2 features of the present group of patients stand out distinctly and suggest that their ultimate clinical course differs in an important way from that of patients with coronary atherosclerosis. First, we have no sign that the function of the heart as an organ is impaired. Although we did not investigate cardiac function in the laboratory in a detailed systematic manner, the complete absence of signs or symptoms of cardiac failure, as well as normal left ventricular filling pressure and angiographic findings, indicates that function is at least not severely impaired. Second, no patient has had clinical or electrocardiographic evidence of myocardial infarction. In 5 patients the chest pain either disappeared or became less severe within 1 to 2 years after the initial study.

Although the available evidence suggests a benign course or perhaps even the absence of a progressive type of heart disease in all but 1 of our patients, we regard the explanation of their chest pain to be unsettled at present and, accordingly, prefer to keep an open mind regarding the eventual clinical outcome in these and other similar cases.

Acknowledgments

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Follow-Up Results of Distal Coronary Artery Bypass for Ischemic Heart Disease

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Statistically significant late results of coronary artery bypass procedures will be unavailable for 5 to 10 years. This report summarizes a critical analysis of the present status of 480 patients followed up for 1 to 30 months after coronary artery bypass. Thirty-day hospital mortality was 6.2 percent and appears to be declining. Arteriographic studies have shown only 1 of 220 patients without at least 1 functioning graft. Graft occlusions appear to be early and technically oriented and ranged from 11 to 14 percent. Significant symptomatic improvement as determined by cardiologists was observed in 92 percent of patients. According to functional classification there was a striking shift from preoperative New York Heart Association classes II, III, and IV, to class I as a result of improved myocardial blood flow. No degenerative changes in autogenous vein bypass grafts have been observed.

Within the past 3 years a most effective treatment for ischemic heart disease, in the form of the distal coronary bypass, has evolved in our hands and other centers.[1–6] The treatment in its basic form consists of complete revascularization of all ischemic peripheral coronary vascular beds by means of reversed saphenous vein bypass segments attached proximally to the ascending thoracic aorta and distally to coronary arteries beyond all significant arteriosclerotic lesions (Fig. 1). Immediate results from this form of therapy have been well documented and include immediate high flow rates with resulting salutory physiologic effects on the ventricular myocardium.[5] Significantly, there has been very low risk compared with previous surgical efforts to revascularize the ventricular myocardium. Furthermore, early evaluation of patency in these distal vein bypass grafts indicates nearly 90 percent to be open, and in our series at least 1 functioning graft was visualized in 99 percent of patients.

The immediate effectiveness of distal coronary bypass with a low operative mortality is now generally recognized. Information regarding long term myocardial function and patient survival is not now available. This fact is readily apparent considering that one of the innovating centers reporting the largest series of early results had never bypassed to the left coronary artery according to a publication dated 1969.[7] Thus, truly long-term results of the distal coronary bypass will not be available from any center for 5 to 10 years. Current appraisal of patients who have undergone the procedure during the past 2½ years is timely and may be predictive of 10 year results. This report therefore presents a critical analysis of the status of 480 patients who had this operation in its pure form, that is without implants, endarterectomy or other forms of revascularization, and who were followed up for 1 month to 2½ years.

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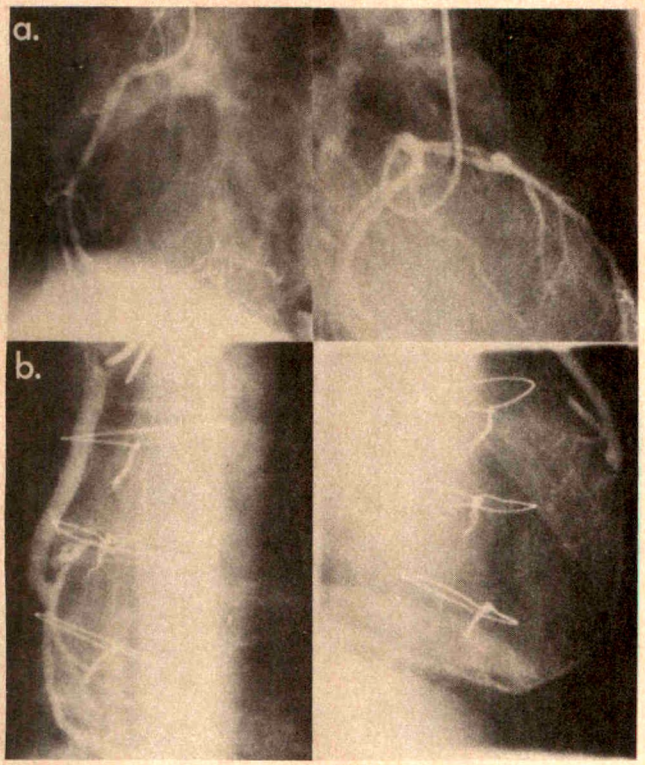

Figure 1. Selective coronary arteriograms of a 46 year old man. **a,** preoperative, showing extreme stenosis in the middle third of the right coronary artery (**left**) and the proximal third of the left anterior descending coronary artery (**right**). **b,** postoperative arteriograms showing vein bypass grafts to right coronary artery (**left**) and to left anterior descending coronary artery (**right**) with bidirectional flow in both segments distal to disease.

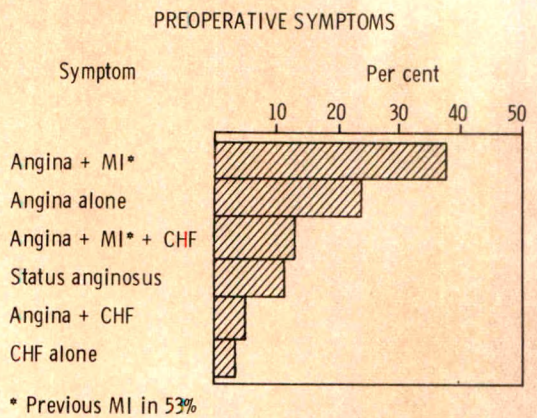

Figure 2. Clinical status of 480 patients before operation. Only 4 percent of patients had no angina and had congestive heart failure (CHF) alone. Previous myocardial infarction was apparent in 53 percent of patients, and congestive heart failure in 22 percent. MI = myocardial infarction.

TABLE I

Severity of Disease

Severity	Patients (%)
Functional classes III and IV	70
At least 3 major coronary arteries significantly stenotic or occluded	62
Major arteries occluded	60
Previous myocardial infarction	53
Increased left ventricular end-diastolic pressure	38
Preoperative congestive heart failure	22

Clinical Material and Methods

In this study 480 patients having undergone aorto-coronary bypass as the sole form of direct myocardial revascularization underwent cardiologic evaluation 1 to 30 months after operation. The average period after operation was 1 year with an 87 percent follow-up rate. All but 4 percent of patients who exhibited congestive failure without pain had angina before operation, and 53 percent had evidence of myocardial infarction (Fig. 2). Severity of preoperative cardiac disease is reflected in the high incidence of patients with functional class III and IV disease (New York Heart Association) (70 percent); with increased end-diastolic pressure (38 percent); and with congestive heart failure (22 percent) (Table I). Age of patients ranged from 23 to 76 years and averaged 50 years. Male patients predominated by a ratio of more than 10 to 1.

Operative technique has been previously described in detail. In summary, it consisted of placement of reversed saphenous vein grafts from the ascending thoracic aorta to 1 or more coronary arteries beyond disease during normothermic total cardiopulmonary bypass with 5 percent dextrose in water dilutional pump prime and ischemic arrest for distal end-to-side anastomoses.[5]

Results of Follow-Up Study

Thirty-day hospital mortality has been steadily declining despite a high and rising percentage of poor risk patients. According to functional class, 30-day mortality ranged from 0 for patients in class I, to 0.8 percent for those in class II, and to 6.3 percent for those in class III, the latter group accounting for almost half of patients. In the salvage group, class IV, the mortality jumped to 12.2 percent (Table II). Similarly, 30-day mortality was related to the number of major coronary arteries appearing at least 50 percent narrowed in preoperative cinearteriograms, ranging from 2.5 percent with 1 vessel involved to 4.2 percent with 2 and 8.0 percent when 3 vessels were diseased. The mortality again sharply increased to 14.1 percent in the salvage group showing 4-vessel involvement (Table III). Late mortality appears low, and the study suggests that it is declining in direct relation to more complete operations (Table IV). In the group of 278 patients followed up from 6 to 30 months, 2.6 percent have died, whereas no deaths have yet occurred in 202 patients followed up for 6 months or less. The trend toward more complete operative revascularization is reflected in the use of single grafts which has declined from 66 percent in the earlier group to 41 percent in the more recent series (Table V).

Symptomatic improvement: Significant improvement with striking relief from preoperative

TABLE II

Relation of Functional Class and Mortality

Class	Patients (%)	Mortality* (%)
I	3	0
II	27	0.8
III	48	6.3
IV	12	12.2

* Overall mortality 6.2 percent.

TABLE III

Relation of Involved Major Arteries to Operative Mortality

Arteries Involved* (no.)	Patients (%)	Mortality (%)
1	13	2.5
2	25	4.2
3	54	8.0
4	8	14.1

* At least 50 percent stenosis or complete occlusion of right coronary, left anterior descending, left circumflex coronary and left main coronary arteries.

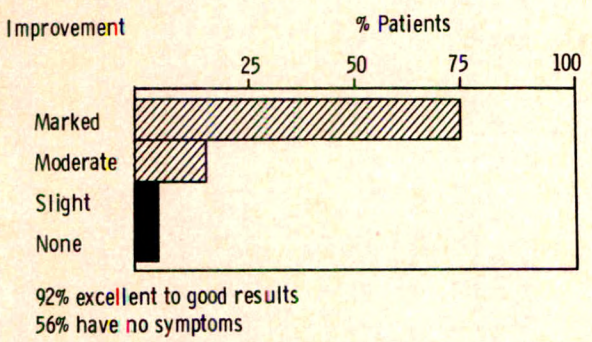

Figure 3. Postoperative improvement as assessed by cardiologist. Complete or significant relief of angina was observed in 92 percent of patients, and 56 percent were completely free of symptoms.

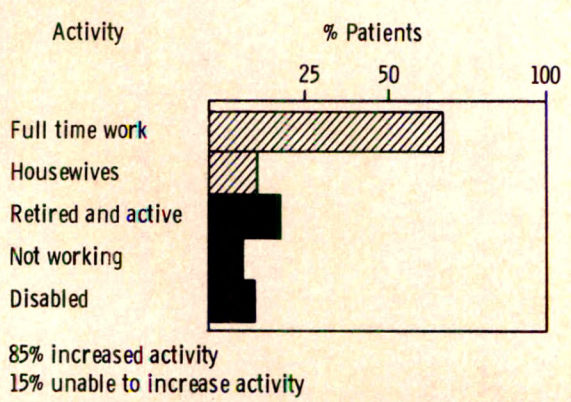

Figure 5. Activity status of 480 patients following coronary artery bypass. Only 15 percent of patients appeared unable to increase activity at the time of follow-up analysis.

TABLE IV

Survival Data

Mortality	Follow-Up Period: 6–24 Months (278 patients)	Follow-Up Period: <6 Months (202 patients)	Total Patients (480)
30 day	6.8%	6%	...
Late	2.6%	...	...
Overall	9.4%	...	6.3%

TABLE V

Increase in Multiple Graft Procedures

Grafts	Follow-Up: 6–24 Months*	Follow-Up: <6 Months†
Single	185 (66%)	84 (41%)
Double	87 (31%)	112 (55%)
Triple	6 (3%)	6 (4%)
Total	278	202

* 278 patients had 377 grafts.
† 202 patients had 326 grafts.

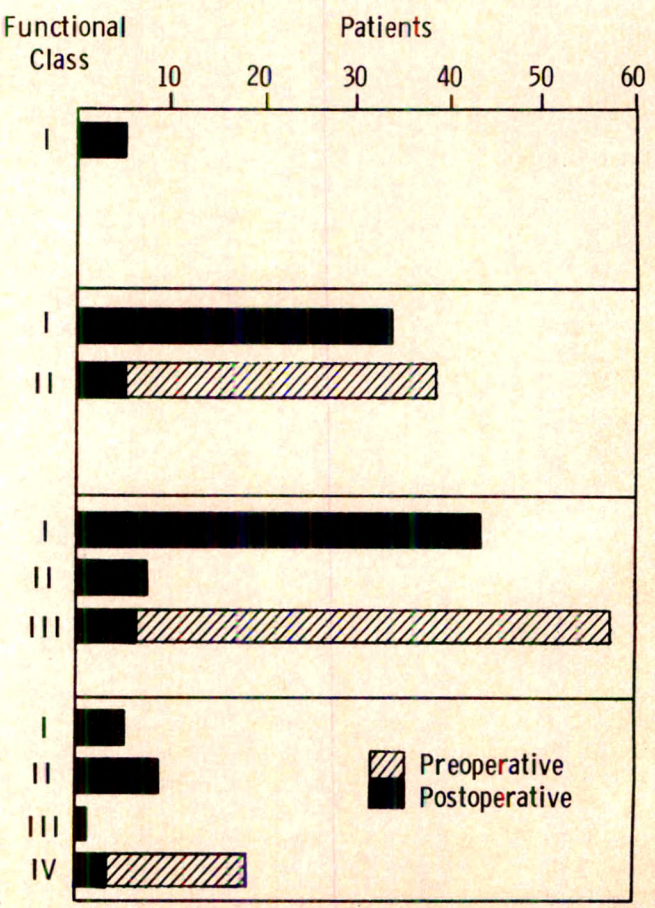

Figure 4. Comparison of New York Heart Association functional class before and after operation. Note the striking upward shift in functional class produced by improved myocardial blood flow in the preoperative classes II, III and IV.

angina, as determined by cardiologists, was observed in 92 percent of patients (Fig. 3). Improvement in functional class following coronary bypass was most significant. Most patients in class II shifted to class I, and the vast majority of patients in class III showed sufficient improvement to be grouped in class I. Similarly, in the salvage catagory of class IV patients, most were considered to be in classes I and II after operation. (Fig. 4).

Postoperative activity had increased significantly in 85 percent of patients at the time of this study, and only 15 percent of patients appeared to be unable to increase their activity (Fig. 5).

Recurrent myocardial infarction: Early nonfatal myocardial infarction within 30 days after operation occurred in 8.2 percent of patients, and fatal infarction in 2.8 percent. Late nonfatal infarction from 30 days to 30 months occurred in 3 percent of patients. However, in the late period, there were 6 deaths which were assumed to be caused by infarction, but there was no postmortem confirmation (Table VI).

Postoperative arteriography: This procedure was performed in 220 patients after coronary artery bypass. Only 1 of these patients was without a single functioning graft, and all other patients studied could be classified as showing improvement from an arteriographic point of view in that at least 1 bypass was open and functioning. However, the percentage of occluded grafts ranged from 11 percent in studies made less than a month after operation to 14 and 13 percent, respectively, for the 12 and 30 months groups (Table VII). In contrast, however, other studies have shown nonpatency rates as high as 23 percent.[8]

Discussion

Truly significant late results of coronary bypass will be unavailable from any center for 5 to 10 years. This study of 480 patients with an average follow-up period of 12 months and a range of 1 to 30 months is all that is available in longer-term analysis, but hopefully will serve a predictive function for true long-term results. The study has shown clearly a low operative mortality for patients with less than 4-vessel involvement and for patients with less than functional class IV preoperative status. For salvage patients with end-stage ischemic heart disease, the mortality has been higher but acceptable and appears to be declining (Tables II to VI). There has been a delayed mortality in only 2.6 percent of patients followed up from 6 to 30 months. Late myocardial infarctions have occurred in only 3 percent of patients. Data on 6 late deaths in which no postmortem studies were available are summarized in Table VIII. At least 4 of the 6 patients had inadequate operations in that not all of the severely narrowed major

TABLE VI

Postoperative Myocardial Infarction

Time	Myocardial Infarcts (%)	
	Nonfatal	Fatal
Operative (30 days)	8.2	2.8
Late (2 years)	3	(6)*
Total	11.2	(10.8)

* Sudden deaths outside the hospital without autopsy.

TABLE VII

Postoperative Arteriograms

Months	Open (%)	Closed (%)	Patients Reoperated Upon*
1	89	11	2
6	88	12	5
12	86	14	1
30	87	13	...

* Severe symptoms returned at time of occlusion.

TABLE VIII

Late Mortality*

Postop. Period (mo)	Age (yr)	NYHA Class	Bypass/ Disease	Operative Complications	Postop. result
1	47	III	1/3	ECG ischemia	Good
1.5	48	II	2/3	MI	Poor
4	49	II	1/1	None	Good
5	52	II	1/2	ECG ischemia	Good
5	39	III	1/1	None	Good
12	55	IV	1/3	None	Fair

* Total late mortality 2.1% to 30 month follow-up.

ECG = electrocardiographic changes of; MI = myocardial infarction; NYHA class = New York Heart Association functional classification; postop. = postoperative.

TABLE IX

Characteristics of Patients Without Improvement

Preop. Symptoms	Duration (mo)	NYHA Class	Bypass/ Vessels	EDP (mm Hg)	Operative Complications
MI/ANG/CHF	108	IV	1/3	26	MI
MI/ANG/CHF	60	III	1/3	6	MI
MI/ANG	36	III	1/3	8	MI
ANG	96	III	1/1	4	Operative
MI/ANG/CHF	73	IV	1/3	21	None
MI/ANG	42	III	1/3	18	None
MI/ANG	62	IV	1/3	17	MI
MI/ANG/CHF	58	IV	2/3	24	None

ANG = angina pectoris; CHF = congestive heart failure; EDP = left ventricular end-diastolic pressure.

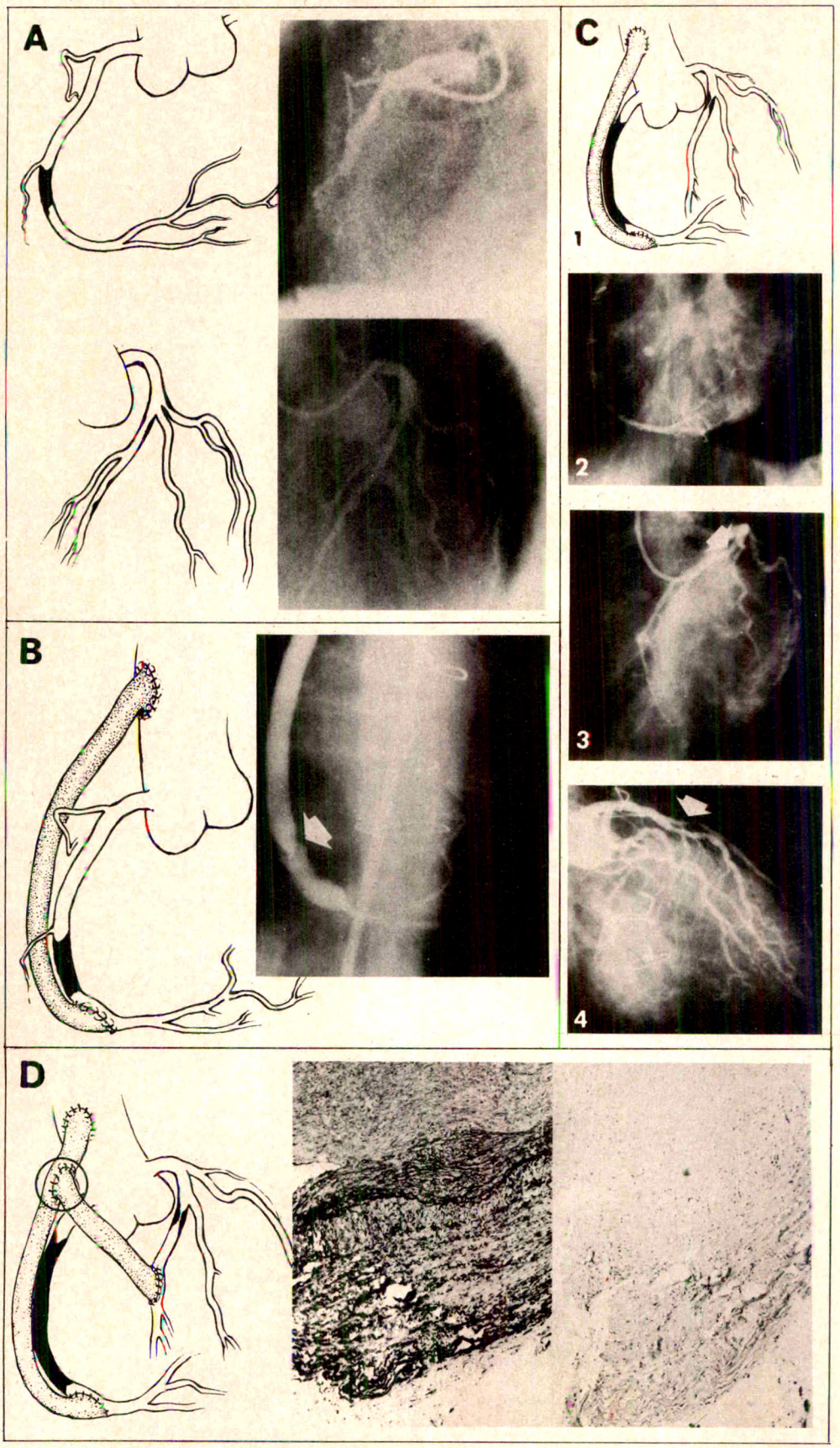

Figure 6. Drawings and selective coronary arteriograms of 52 year old man. **A,** preoperative, showing complete occlusion of right coronary artery and 10 percent narrowing of the proximal left anterior descending coronary artery. **B,** 10 days after distal right coronary bypass. Note visualization of venous valve and lack of arterialization of graft. **C,** 2 years after operation. Patient returned because of 2 month history of increasing angina. Note absence of previously visualized venous valve and obvious arterialization of bypass graft (**2**). Angina had recurred after 22 months as the result of progression of 10 percent stenosis to 90 percent stenosis in left anterior descending coronary artery (**see arrows**). **D,** Drawing and photomicrographs showing source of biopsy material and arterialization of vein graft 2 years after operation. Elastic tissue stains and hematoxylin and eosin stains show appearance of normal artery wall. After secondary operation with bypass to left anterior descending coronary artery the patient became asymptomatic.

coronary arteries were bypassed. Similarly in analyzing data in 8 patients showing no functional improvement, all had incomplete operations except 1 who had an operative complication (Table IX). Furthermore, 6 of the 8 had the operative complication of myocardial infarction, and all were in preoperative classes III and IV. Their findings suggest that failure tends to be the result of incomplete operation or technical error.

Arteriographic evidence of graft occlusion varied from 11 percent in studies made within a month after operation to 14 and 13 percent, respectively, at 12 and 30 month periods of follow-up (Table VII). The very small addition of 2 to 3 percent occlusions in the early and late arteriograms suggests that late occlusions are rare and that most graft occlusions occur early and are technically oriented. Only 1 of 220 patients failed to exhibit at least 1 functioning bypass graft. Late arteriograms and biopsy specimens show arterialization of the vein grafts and no degenerative changes in the grafts have been noted (Fig. 6).

Follow-up appraisals of patient activity shows that only 15 percent were not helped in this aspect, and most of these patients had been in functional class IV preoperatively (Fig. 5). Hence, even these patients with no increase in activity may have been helped in respect to survival. Probably the most striking finding in this study has been the upward change in functional classification of the patients in preoperative classes III and IV (Fig. 4). With few exceptions, the functional classification of these patients was converted to classes I and II by coronary artery bypass.

Addendum

Since submission of this manuscript, an additional 1,400 patients have undergone coronary artery bypass procedures. Two patients have returned with evidence of intimal and medial hyperplasia of the vein graft.

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Open Heart Surgery for Acquired Heart Disease in Jehovah's Witnesses

A Report of 42 Operations

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Patients belonging to the Jehovah's Witness faith may present a special problem when undergoing open heart surgery since they steadfastly refuse blood transfusion. Using a bloodless prime technique of extracorporeal circulation, we performed during an 8-year period 42 open heart operations for acquired heart disease in a consecutive series of 40 patients who were Jehovah's Witnesses. Three patients (7 percent) died, and only 1 death was caused by anemia. The favorable results we attribute in part to the brief periods of cardiopulmonary bypass used. In more than 70 percent of cases pump time was less than 40 minutes. We believe that our experience demonstrates the feasibility of open heart surgery in Jehovah's Witnesses and, moreover, indicates that blood transfusion can and should be used sparingly to reduce morbidity and mortality in all patients.

> "Every moving thing that liveth shall be meat for you . . . but flesh with the life thereof, which is the blood thereof, shall ye not eat." (Genesis 9:3,4)

Literal interpretation of this and other similar Biblical passages has caused many patients belonging to the Jehovah's Witness faith to refuse blood transfusion in the belief that it is a sin against God, and thus deny themselves the benefits of open heart surgery. This religious sect originated in 1870 in a small Bible study class in Allegheny, Pa. All members are preachers, and their evangelistic work has resulted in phenomenal growth. The faith is now represented in 193 countries, has a worldwide membership of more than 1,250,000 and numbers more than 343,000 members in the United States alone.[1] Fundamentalists by nature, the Jehovah's Witnesses derive all matters of policy from scriptural sources—even their name, which was conceived from the Bible passage: "Ye are my witnesses, saith the Lord . . ." (Isaiah 43:10). Their steadfast refusal of blood transfusion, which they regard as an actual "eating of blood" (in the same manner that an infusion of glucose solution provides nourishment), is based on a literal interpretation of Biblical references such as the following:

> "And whatsoever man . . . that eateth any manner of blood; I will even set my face against that soul that eateth blood, and will cut him off from among his people. For the life of the flesh is in the blood; and I have given it to you upon the altar to make an atonement for your souls; for it is the blood that maketh an atonement for the

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soul. Therefore I said unto the children of Israel, no soul of you shall eat blood." (Leviticus 17:10–14)

Jehovah's Witnesses rarely depart from their religious beliefs by accepting blood transfusion, even when the alternative is death. The surgeon unwilling to treat these persons on the terms of their faith should not accept them as patients. To administer a transfusion to such patients against their wishes could imply bodily assault and constitute a violation of their rights.[2–5]

The advent of hemodilution techniques for cardiopulmonary bypass using a bloodless prime has allowed these patients safe repair of cardiac defects without blood transfusion. Since 1962 bloodless prime has been routinely utilized in more than 5,000 operations at this institution with excellent results; and several hundred of these operations were performed electively without blood transfusion in patients most of whom were not Jehovah's Witnesses.[6,7]

In this report we detail our experience with 42 open heart operations for acquired heart disease performed on 40 Jehovah's Witnesses without using blood.

Method

Hemodilution perfusion has been used since 1962 at this institution and was employed in all cases in this study.[6,7] The priming volume of a Travenol bag or Bentley Temptrol oxygenator consisted of 20 to 30 ml of 5 percent dextrose solution per kilogram of body weight, with 25 mg of heparin added per 1,000 ml of priming solution. Normothermia was maintained during perfusion. Upon completion of bypass, all the blood in the extracorporeal unit was slowly returned to the patient.

The Jehovah's Witness patients in this series received the same treatment as all other patients except that all Witness patients received injectable iron before and after operation, and no blood was held in reserve for them at the blood bank. The only fluid they received was the priming solution and intravenously administered dextrose in dilute saline or Ringer's lactate solution. Dextran was used in only 1 patient, who had prolonged excessive bleeding after surgery and subsequently died.

Case Material

From May 16, 1962 to May 15, 1970, 42 open heart operations for acquired heart disease were performed without blood transfusion on 40 Jehovah's Witnesses. The patients ranged in age from 29 to 69 years (average 42 years). Most patients underwent mitral valve replacement (13 cases) or aortic valve replacement (12 cases). Other operations included double and triple valve surgery, mitral annuloplasty, bilateral aortocoronary bypass, and left ventricular aneurysmectomy (Table I). In more than 70 percent of cases less than 40 minutes of perfusion time was required for surgical correction.

TABLE I

Results of 42 Open Heart Operations for Acquired Heart Disease in 40 Jehovah's Witnesses

Procedure	Patients (no.)	Deaths (Mortality) (no.)	Duration of Total Cardiopulmonary Pump Time (range in min)
Mitral valve replacement	13	1 (8%)	18–39
Aortic valve replacement	12	0	30–43
Double valve surgery	9	2 (22%)	37–60
Mitral annuloplasty	5	0	11–21
Triple valve surgery	1	0	60
Bilateral aortocoronary bypass	1	0	72
Repair left ventricular aneurysm	1	0	19
Total	42	3 (7%)	

Results

Mortality for the entire series was 7 percent or 3 deaths, and it was greatest (22 percent) in the 9 patients who had double valve surgery (Table I). One of these, a 29 year old man, died from myocardial insufficiency, a few days after operation. His hematocrit at the time of death was 39 percent. Another patient, a 47 year old woman with embolism to the right cerebral artery causing left hemiplegia, died of pneumonia 18 days after aortic and mitral valve replacement. A thrombus was discovered in the left atrium at operation. The third death was the only one attributed to anemia. It occurred in a 52 year old man who had a cardiac arrest 3 days after mitral valve replacement. His hematocrit was 23 percent at the time of death. The average hematocrit 1 week after surgery for all 40 patients was 34 percent.

Discussion

Since 1962 we have routinely employed hemodilution techniques with bloodless prime for open heart surgery.[7] The bloodless prime technique has the practical advantage of conserving the limited amounts of blood in banks and hospitals, reducing the cost of operation to the patient and making open heart surgery more readily available in emergencies. Complications that may occur as a direct result of blood transfusion are well known.

Homologous blood syndrome: Bloodless prime is beneficial to renal function of the patient since it creates a profound diuresis after return of prime volume, favoring improved renal function during the early postoperative period. Obviously, renal failure secondary to mismatched blood groups or other factors is eliminated by avoiding blood transfusion. Many complications of early

open heart operations were actually due to using large volumes of pooled blood. Gadboys et al.[8] reported a "homologous blood syndrome" associated with significant morbidity observed in cases in which pooled homologous blood was used for priming the extracorporeal system. This was further studied by Hegarty and Stahl,[9] who found that a specific sensitivity reaction at the capillary level and increased capillary permeability cause loss of fluid and protein into the extracellular space. The resultant increase in pulmonary vascular resistance may lead to reduced pulmonary perfusion and systemic circulatory collapse. One of the factors in homologous blood syndrome may be transmission of antigens from previous blood transfusions. Perkins et al.[10] reported the massive hemolysis of donor red cells occurring because of isoimmunization even though isoantibodies were not detected before operation. The antibody subtype must be identified before further blood is administered in such cases.

In addition to problems in matching and isoimmunization, other factors may cause complications in patients receiving large volumes of pooled homologous blood during open heart surgery. For instance, McNamara and co-workers,[11] while caring for combat casualties, found a significant amount of fibrin, red cell aggregates and platelet debris in stored blood, but not in fresh whole blood. This debris can easily pass the filters of most blood transfusion sets and result in pulmonary microembolism.

Post-transfusion hepatitis and clotting abnormalities: The use of a bloodless prime has reduced the incidence of post-transfusion hepatitis, currently reported as 6 percent per unit of commercial bank blood.[12] At some medical centers where large volumes of blood are used to prime the bypass units, the incidence of hepatitis has been as high as 51 percent.[13] In 1 series of patients who underwent open heart operations requiring blood transfusion, mortality from serum hepatitis alone was 11.2 percent—more than the overall mortality for those with acquired heart disease reported on herein.[14] Blood-borne diseases such as malaria and syphilis have also occurred, although rarely, as a result of transfusion.

Recently, fresh heparinized blood has been incriminated in transferring a cytomegalovirus, the virus causing cytomegalic inclusion disease which has serious and often fatal results in infants and children.[15] The post-perfusion syndrome characterized by the delayed onset of fever, lymphocytosis and splenomegaly is another complication for which the use of blood may be responsible.[16]

Abnormalities of coagulation may cause hemorrhage and should be avoided especially in the Jehovah's Witness. Patients previously receiving anticoagulant agents must be carefully prepared with vitamin K. Clotting abnormalities are decreased when less blood is used for cardiopulmonary bypass. In a study by Cuello et al.[17] of the total serosanguineous output through chest catheters during the first 24 hours after operation, patients who received dextrose and water prime had a lower overall amount of chest drainage than those who received blood and dextran prime.

Bypass time: According to Porter et al.[18] clotting abnormalities increase with bypass time. After 1 hour of cardiopulmonary bypass the platelet count, prothrombin and factor V are considerably decreased. Fibrinogen decreases more slowly, and fibrinolytic activator activity increases in linear fashion with bypass time. Since every possible safeguard should be taken to avoid excessive blood loss in the Jehovah's Witness, we believe that the duration of cardiopulmonary bypass should be kept as short as reasonably possible. In 39 of our 42 cases bypass time was less than 1 hour. This shortened bypass time together with exacting hemostasis and total correction of the cardiac lesion contributed significantly toward the successful results obtained in these patients.

Dextran: We did not use dextran in the priming solution because it remains longer in the vascular compartment than does 5 percent dextrose and water. Low molecular weight dextran has an intravascular half life of about 14 hours and could cause prolonged hemodilution and hypervolemia when the patient's blood is returned at completion of operation. Hypervolemia taxes cardiac function and may contribute to failure in patients with a compromised myocardium. In addition, low molecular weight dextran increases the bleeding time and decreases the fibrinogen content, which does not return to normal for 24 hours. It may also cause allergy and anaphylactic reactions.

All of our patients were given iron therapy before and after surgery to enhance erythropoiesis.

Epsilon-amino-caproic-acid (EACA) has been advocated as a prophylaxis for reducing postoperative bleeding, and it is effective in inhibiting plasminogen activator substance and, to a lesser degree, plasmin activity.[19] Several patients in this series received EACA.

Vascular surgery: Recently we reported our experience with 20 Jehovah's Witnesses who underwent central or peripheral vascular surgery for congenital or acquired disease.[20] Only 2 of these patients died, 1 of whom was 74 years old. In the other patient death occurred after a subsequent open heart operation. Results in this series compared favorably with results in other patients, not Jehovah's Witnesses, undergoing similar operations, indicating that a good outcome can be obtained in vascular surgery without using blood transfusion.

Clinical implications: Successful accomplishment of open heart operations without blood transfusion is not unusual. From December 3, 1969 to

January 30, 1970, 100 consecutive cases of open heart surgery in other patients at this institution required a total of only 141 units of blood (including blood used during the entire hospital stay of each patient). In 35 cases no blood was used; and in 31, only 1 unit was administered. The average transfusion requirement was less than 2 units of blood, even though 2 patients received 10 units each. Thus, the Jehovah's Witness patient undergoing open heart surgery does not necessarily present a special problem at this institution, since we are routinely cautious in administering blood. Admittedly, the Jehovah's Witness patient foregoes the added safeguard of having blood on standby in case it is needed. Generally, however, such a patient can face an open heart operation without blood transfusion with the assurance of favorable results.

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Hypoplastic Left Heart Syndrome

Clinicopathologic and Hemodynamic Correlation

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Eleven patients with the hypoplastic left heart syndrome, defined as atresia of the aortic or mitral valve, or both, with normally related great arteries and intact ventricular septum, were studied. There were 2 clinical groups. Group I (8 cases) comprised patients with early distress, ashen cyanosis and feeble or absent peripheral pulses in the presence of a hyperdynamic precordium and death in the first week of life. Group II (3 cases) comprised patients with good peripheral pulses, marked cyanosis and survival for more than 1 week. All of the patients had characteristic electrocardiographic and radiographic findings. In Group I, values for pulmonary oxygen saturation were elevated with pressures moderately increased, whereas in Group II, oxygen saturation values were greatly lowered with markedly increased pressures. All patients had hypoplastic ascending aorta, large patent ductus arteriosus and diminutive left ventricle, left atrium and foramen ovale. Three of 8 had abnormalities of the coronary sinus. A positive correlation can be made between the clinical appearance and the hemodynamic findings which may allow selection for palliative surgical procedures.

The hypoplastic left heart syndrome as described in this report refers to patients having aortic or mitral valvular atresia, or both, with normal relation of the great arteries and intact ventricular septum. This condition is universally fatal in early infancy, and successful palliation or medical management is virtually impossible at present. This communication presents our experience with this unusual defect in order to emphasize the correlation between the clinical, pathologic and hemodynamic findings and their relevance in respect to palliative surgical attempts.

Clinical Material

Eleven patients studied between April 1966 and November 1970 form the clinical material. Nine of the patients were seen during life at the Medical College of Georgia. The hearts and clinical data of 2 patients, a pair of twins seen at another hospital, are included. These 2 infants were related to another of our clinic patients who had the angiographic appearance of mitral atresia, transposition of the great arteries with pulmonary stenosis and ventricular septal defect.

In addition to this family, 3 other patients had a family history of congenital heart disease. A first cousin of Patient 2 was diagnosed as having congenital heart disease, and he died shortly after birth. A paternal aunt of Patient 5 died of a congenital heart malformation at age 3 days, and a maternal granduncle was diagnosed as having an atrial septal defect. A paternal uncle of Patient 8 had an operation for coarctation of the aorta and a maternal granduncle died at age 2 years with the diagnosis of cyanotic congenital heart disease.

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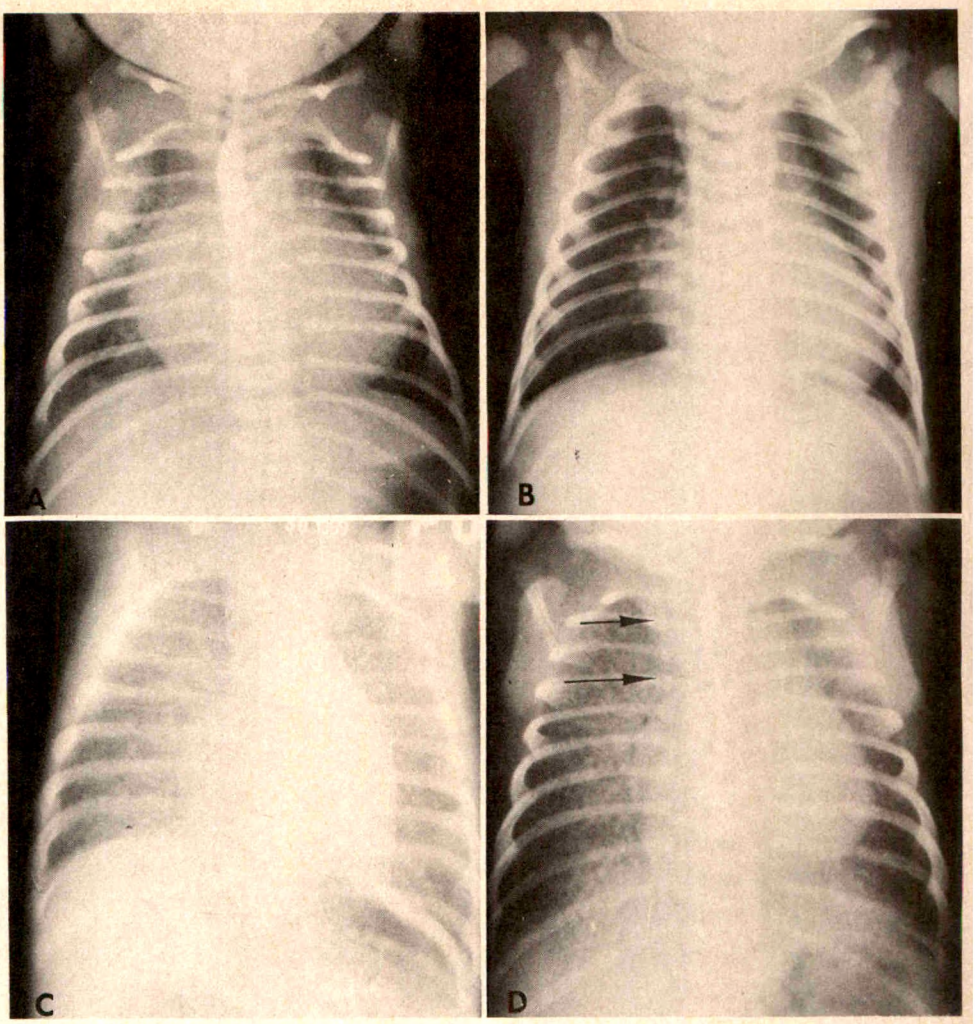

Figure 1. Frontal chest radiograms: Cases 2 (**A**), 6 (**B**), 9 (**C**) and 11 (**D**). **A** and **B** belong to clinical group I. Note cardiomegaly and increased pulmonary vascular markings. **C** and **D** are from clinical group II. Arrows (**D**) indicate the reversed "5" appearance caused by absence of the ascending aorta obvious in 5 cases.

Results

There were 7 patients with aortic valvular atresia all of whom had hypoplasia of the mitral valve, and 4 patients with combined mitral and aortic valvular atresia (Table I). Nine patients were male; 6 were Caucasian and 5 were Negro. There were no survivors. The age at the time of death was 24 hours to 10 weeks.

Between 4 and 72 hours of age, 10 infants showed recognizable illness consisting of respiratory difficulty with duskiness or cyanosis after a variable symptom-free period. According to the clinical and hemodynamic findings, there were 2 groups of patients. Group I (8 cases) comprised patients who had a rapidly fulminant course and died within the first week of life; in 7 of the 8 infants death occurred before age 72 hours. The most striking physical finding in this group was the combination of a hyperdynamic precordium with feeble or absent peripheral pulses and a dusky cyanosis. A grade 2–3/6 systolic ejection murmur was described in 5 cases. Group II (3 cases) comprised patients who, although symptomatic, survived beyond age 1 week. All the subjects in this group were described as having fair to good peripheral pulses, a systolic ejection murmur, grade 2–3/6 and a more intense degree of cyanosis. None showed evidence of shock until they reached the terminal state, when a state of peripheral vasomotor collapse with the typical dusky discoloration of the lips and nailbeds was noted.

Chest roentgenograms (Fig. 1): These were obtained in 10 cases. Cardiomegaly was a constant finding with a cardiothoracic ratio ranging between 0.55 and 0.68. An interesting radiographic observation in all patients of group II and in at least 2 of those in group I was a peculiar angulation at the area of junction of the superior vena caval and the right atrial shadows in the frontal projection. This gave the right cardiac silhouette the appearance of a reversed "5" that was more prominent when there was marked right atrial enlargement. All patients had increased pulmonary vascularity, arterial as well as venous, which was extreme in infants in acute distress. Pulmonary venous engorgement was a prominent and con-

TABLE I

Clinical Summary of 11 Cases

Case no.	Race & Sex	Age: Onset	Age: Death	Physical Findings	Electrocardiogram	X-Ray Findings	Catheterization	Autopsy
Group I. Infants Who Survived Less Than 1 Week								
1	NM	24 hr	36 hr	Cyanosis; active precordium	...	Cardiomegaly; CT 0.60; increased PVM	...	Aortic valve atresia; mitral valve atresia; diminutive LA; patent foramen ovale; hypoplastic coronary sinus; large PDA
2	WM	2 days	5 days	Cyanosis; systolic murmur 2/6; active precordium; feeble pulses	RAD; RAH; RVH; rR in V_1; rRs in V_6	Cardiomegaly; CT 0.65; increased PVM	RA, LA and RV pressures increased; small left atrium; RV enlarged; bidirectional shunt	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; patent foramen ovale; large PDA
3	WM	4 hr	2 days	Cyanosis; systolic murmur 3/6; active precordium	RAD; qR in V_1; rRs in V_5–V_6	Cardiomegaly; CT 0.55; increased PVM	...	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; patent foramen ovale; absent coronary sinus; large PDA
4	NM	6 hr	30 hr	Grey pallor; systolic murmur 2/6; active precordium; pulses absent	RAD; RVH; rRs in V_1; rsRs V_5–V_6	Cardiomegaly; CT 0.55; increased PVM	...	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; patent foramen ovale; large PDA
5	WM	24 hr	72 hr	Grey pallor; systolic murmur 2/6; active precordium; pulses absent	RAH; RVH; RS in V_1; RS in V_5–V_7	Cardiomegaly; CT 0.60; increased PVM	RA, LA and RV pressures increased; small left atrium; RV enlarged; bidirectional shunt	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; patent foramen ovale; vestigial coronary sinus with atresia of the orifice
6	NM	24 hr	72 hr	Cyanosis	...	Cardiomegaly; CT 0.60; increased PVM	...	Aortic valve atresia; mitral valve atresia; diminutive LA; patent foramen ovale; large PDA
7	NM	30 hr	72 hr	Cyanosis	...	...	...	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; patent foramen ovale; large PDA
8	NF	24 hr	72 hr	Grey pallor; systolic murmur 3/6; active precordium; feeble pulses	RAD; RVH; rRs in V_1; rR in V_5–V_7	Cardiomegaly; CT 0.65; increased PVM	RA and RV pressures increased; RV enlarged; bidirectional shunt	Aortic valve atresia; mitral valve atresia; patent foramen ovale; large PDA

Group II. Infants Who Survived Longer Than 1 Week

9	WM	1 wk	10 wk	Cyanosis; systolic murmur 2/6; active precordium; weak pulses; single S_2	RAD; RAH; RVH; rsRs in V_1; rRS in V_5–V_6	Cardiomegaly; CT 0.66; increased PVM	RA and RV pressures increased; small LA; enlarged RV; bidirectional shunt	Aortic valve atresia; mitral valve hypoplasia; patent foramen ovale; EFE of the LV; large ductus arteriosus
10	WM	1 day	18 days*	Cyanosis; systolic murmur 3/6; active precordium; good pulses; single S_2	RAD; RAH; RVH; rsR in V_1; rS in V_5–V_7	Cardiomegaly; CT 0.60; increased PVM	RA and RV pressures increased; enlarged RV; predominant right to left shunt	Aortic valve atresia; mitral valve hypoplasia; diminutive LA; tunneled foramen ovale; EFE of LV; large ductus arteriosus
11	WF	1 day	9 days	Cyanosis; systolic murmur 2/6; active precordium; good pulses; single S_2	RAD; RAH; RVH; rsR in V_1; rR in V_5–V_7	Cardiomegaly; CT 0.63; increased PVM	RA and RV pressures increased; enlarged RV; predominant right to left shunt	Aortic valve atresia; mitral valve atresia; diminutive LA; fenestrated foramen ovale; large ductus arteriosus

* Aspirated.
CT = cardiothoracic ratio; EFE = endocardial fibroelastosis; LA = left atrium; LV = left ventricle; NM = negro male; PDA = patent ductus arteriosus; PVM = pulmonary vascular markings; RA = right atrium; RAD = right axis deviation; RAH = right atrial hypertrophy; RV = right ventricle; RVH = right ventricular hypertrophy; WF = white female; WM = white male

stant finding in all of those who survived longer than 1 week.

Electrocardiograms (Fig. 2): These were taken in 8 cases and revealed a QRS axis between +90° to +210°. All 8 patients had right ventricular hypertrophy, and 2 had a pattern of right bundle branch block. Right atrial hypertrophy was present in 6. The QRS loops in the frontal as well as the horizontal planes were clockwise in all. Q waves were consistently absent in the left precordial leads, and in no instance could the left ventricle be identified by pattern although the R wave voltage appeared significantly increased ("pseudo left ventricular hypertrophy") in 7 cases.

Cardiac catheterization and cineangiocardiography: These procedures were performed in 6 cases, 3 patients in group I and all 3 in group II (Table II). The cases from group I had elevated values for oxygen saturation in the right heart chambers and pulmonary to systemic flow ratios consistently greater than 1. In all patients, systolic pressure in the right ventricle and pulmonary artery was less than 75 mm Hg. Patients in group II had very low values for right-sided and systemic oxygen saturation, a pulmonary to systemic flow ratio less than 1, and systolic right ventricular and pulmonary arterial pressure greater than 75 mm Hg. Pulmonary vascular resistance appeared to be significantly increased in all patients of group II. The right ventricle and the main pulmonary artery were markedly enlarged, and the ductus arteriosus had a caliber similar to that of the descending aorta in all cases. No patient had a significant gradient between the descending aorta and the main pulmonary artery. Retrograde flow from the aortic arch to the root of the ascending aorta and coronary arteries could be demonstrated angiographically (Fig. 3).

Autopsy (Fig. 4): All the hearts had a small patent foramen ovale ranging from 1.0 to 5.0 mm in diameter. All had enlarged right heart chambers and a rudimentary left ventricle. Nine had an extremely small left atrium. One of the patients with a sizable left atrium survived for 10 weeks. The ductus arteriosus was found to be universally patent, and in all was of a caliber closely approximating that of the descending aorta. In no instance was there evidence to indicate that the ductus was undergoing closure. The ascending aorta was diminutive and patent in all and gave rise to the coronary arteries in a normal fashion. Five hearts had a ridge similar to that found in coarctation of the aorta at the point where the ascending aorta joined the arch. In 3 there was endocardial fibroelastosis of the left ventricle. Abnormalities of the coronary venous drainage were found in 3 of the 8 patients whose atria were suitable for this examination. The heart in Case 1 showed hypoplasia of the coronary sinus. In Case 3, the coronary veins drained directly to the right atrium

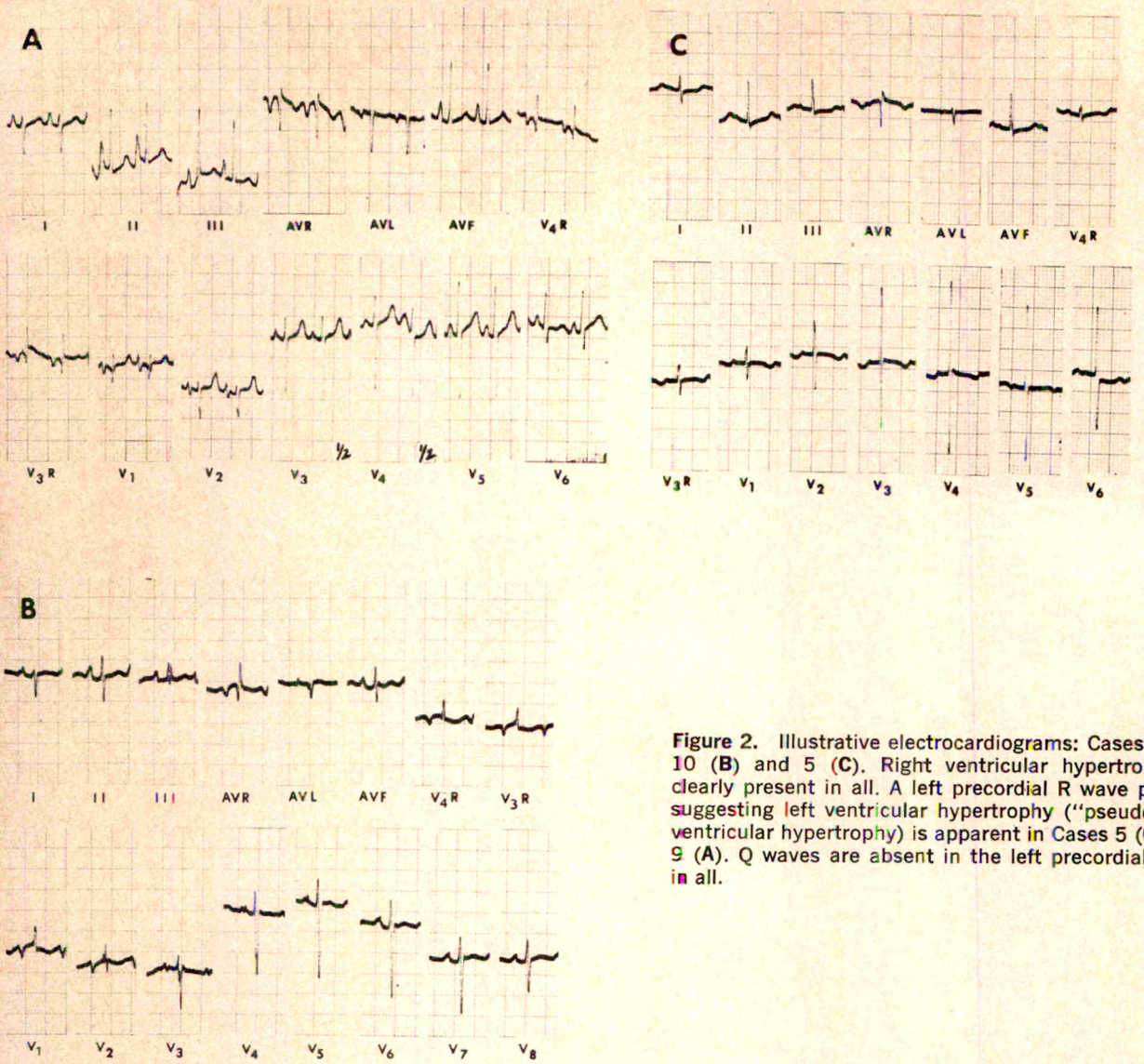

Figure 2. Illustrative electrocardiograms: Cases 9 (**A**), 10 (**B**) and 5 (**C**). Right ventricular hypertrophy is clearly present in all. A left precordial R wave pattern suggesting left ventricular hypertrophy ("pseudo" left ventricular hypertrophy) is apparent in Cases 5 (**C**) and 9 (**A**). Q waves are absent in the left precordial leads in all.

TABLE II

Cardiac Catheterization Findings in 6 Cases

	Group I						Group II					
	Case 2		Case 5		Case 8		Case 9		Case 10		Case 11	
Position	O_2 Sat. (%)	Pressures (mm Hg)	O_2 Sat. (%)	Pressures (mm Hg)	O_2 Sat. (%)	Pressures (mm Hg)	O_2 Sat. (%)	Pressures (mm Hg)	O_2 Sat. (%)	Pressures (mm Hg)	O_2 Sat. (%)	Pressures (mm Hg)
VC	46	...	83	...	39	...	32	...	30	...	25	...
RA	84	a = 15; v = 15	95	a = 17; v = 12	79	a = 18; v = 24	58	a = 7; v = 3	39	a = 12; v = 8	30	a = 6; v = 8
RV	86	50/4/14	96	48/2/14	89	67/2–8/23	57	83/0/6	36	80/0/8	30	75/0/6
MPA	...	...	95	30/18	...	...	52	86/50	38	84/50	33	75/
AO	...	...	...	...	...	...	52	84/50	38	80/45	33	70/40
QP:QS ratio		4:1		5:1		6:1		1:5		1:6		1:4
Age		4 days		1 day		1 day		2 months		8 days		5 days

AO = aorta; MPA = main pulmonary artery; QP = pulmonary blood flow; QS = systemic blood flow; RA = right atrium; RV = right ventricle; Sat. = saturation; VC = vena cava.

without any evidence of a coronary sinus. In Case 5 there was a vestigial coronary sinus with atresia of the orifice and no apparent outlet to either atrium.

Discussion

Isolated cases of hypoplastic left heart syndrome were initially described by a variety of terminologies.[1–4] However, in 1952 Lev[5] described a group of patients with anatomic changes consistent with underdevelopment of the left-sided chambers and termed this spectrum of malformations *hypoplasia of the aortic tract complexes*. Noonan and Nadas[6] later classified cases with aortic arch atresia or hypoplasia. Recently, Sinha et al.[7] proposed the term *hypoplastic left ventricle syndrome*, indicating that the basic abnormality is in the left ventricle. Confusion still exists because of the lack of uniform nomenclature and classification of the abnormality. In the present report, we have included only atresia of the aortic or mitral valves with intact ventricular septum and normally positioned great vessels.

Although an uncommon defect, hypoplastic left heart syndrome nonetheless is a highly significant cause of cardiac neonatal death, exceeding transposition of the great vessels in the series reported by Lambert et al.[8] and ranking with transposition as a cause of cyanosis and congestive heart fail-

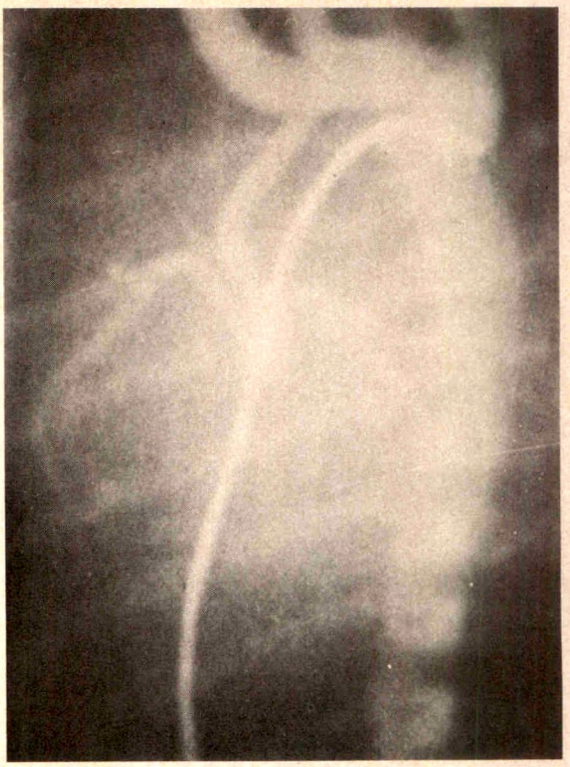

Figure 3. Case 11. Single frame from retrograde cineaortagram in left anterior oblique projection. Injection in descending aorta with catheter through the ductus arteriosus. Note retrograde opacification of the diminutive ascending aorta and coronary arteries.

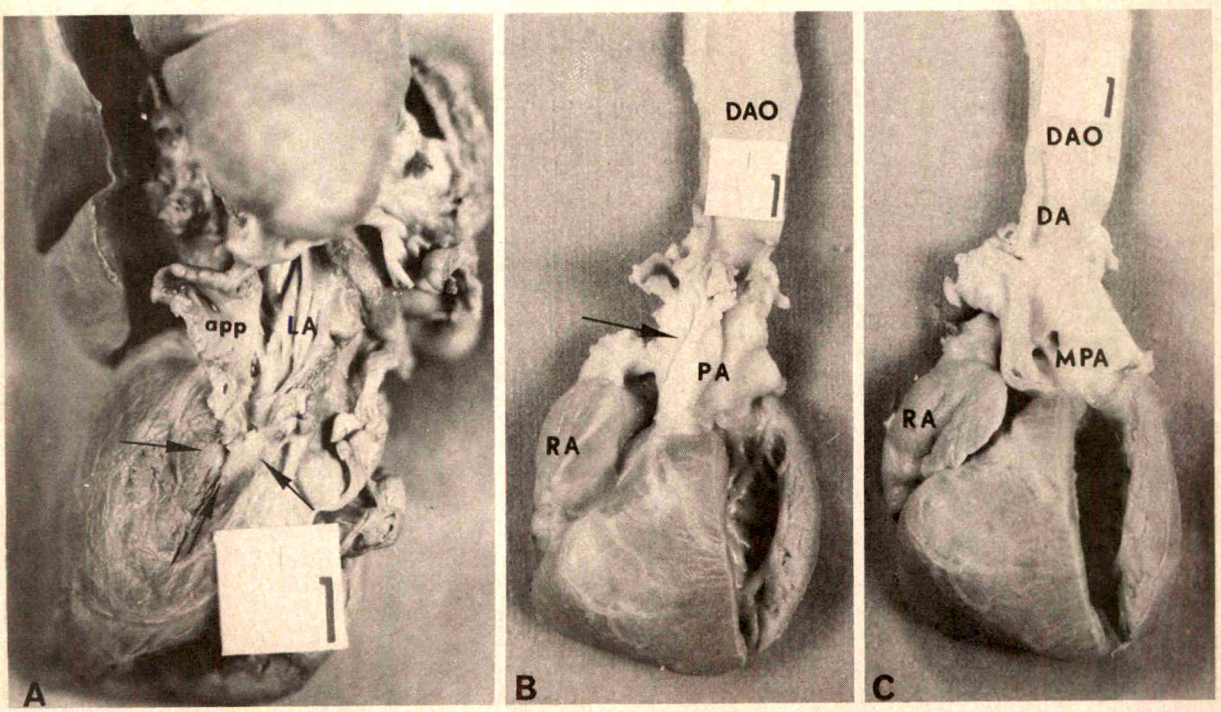

Figure 4. Case 6. Specimens of heart. Marker is 1 cm in all illustrations. **A,** View from posterior with left atrium (LA) and left ventricle exposed. The diminutive body of the left atrium approximates its appendage (app) in size. **Arrows** indicate the tiny left ventricle. **B,** Anterior exposure showing the greatly enlarged right atrium (RA) and opened right ventricle. The pulmonary artery (PA) is not opened. **Arrow** indicates the diminutive ascending aorta as it courses to communicate with the descending aorta (DAO). **C,** Same exposure as (**B**) but with main pulmonary artery (MPA) opened. Note absence of change of caliber between the main pulmonary artery, ductus arteriosus (DA) and descending aorta (DAO).

ure in the first weeks of life.[9–13] This communication was not intended to include speculation on the origin of the condition, but the presence of a positive family history in 5 of the 11 cases, as well as the occurrence in a set of twins who may have been identical, is noteworthy. The characteristics of gross chromosomal abnormalities were not apparent in any cases, and chromosomal studies were not performed on these patients. As with the present series, the infant with hypoplastic left heart syndrome is usually male especially when there is aortic valvular atresia, and this predominance is usually greater than 2:1.[6,7,14–18]

Clinical Features

The onset of symptoms is most closely related temporally to the predictable reduction in pulmonary vascular resistance. Thus, at birth and as long as pulmonary vascular resistance is increased, the right ventricle is essentially a "systemic" ventricle, and perfusion of the systemic bed is adequate. As pulmonary vascular resistance declines in the early postnatal period, the right ventricle becomes principally a "pulmonary" ventricle; there is a decrease in the blood flow through the ductus arteriosus; and systemic flow falls precipitously, giving a shock-like appearance. Thus, a great amount of blood is "sequestered" in the pulmonary circulation and unavailable to the systemic circulation. The infant becomes pale and pulseless with radiographic evidence of pulmonary venous engorgement.

The patients that constitute clinical group II were capable of maintaining an increased pulmonary vascular resistance and, hence, an adequate systemic blood flow for longer periods of time; they were able to survive as long as they could maintain a circulatory pattern approximating that seen during fetal life. We emphasize that in no instance was ductal closure clinically or hemodynamically apparent and, as mentioned, all ductus were widely patent at autopsy. Thus, the collapsing, shock-like state appears to be entirely due to the changes in pulmonary vascular resistance and not to interruption of systemic flow due to ductus closure.

As indicated by the cineangiocardiograms, coronary perfusion is probably poor, even when aortic perfusion is sufficient, due to the extreme underdevelopment of the ascending aorta; a state of myocardial hypoxia probably exists throughout life, thus further contributing to the terminal shock-like state. Other factors that play a definite role are hypoxia and acidosis, overload of the right ventricle and the relative obstruction to pulmonary venous return imposed by the abnormally diminutive left atrium.[19,20] Recent reports[21–23] indicate that patients with hypoplastic left heart syndrome live in a state of generalized systemic underperfusion that becomes evident by pathologic changes in the liver, pancreas, adrenal glands and central nervous system.

The typical radiographic findings reflect the altered physiologic features in most patients by revealing cardiomegaly, increased pulmonary vascular markings, and evidence of pulmonary venous congestion. The radiographic finding of a reversed "5" in respect to the right cardiac border appears to be due to the absence of the shadow of the ascending aorta. This finding was less evident in the patients of group I, probably because there was superimposition of the thymic shadow since the chest X-ray films were taken in the first 48 hours of life.

The most striking electrocardiographic finding in all cases was the absence of Q waves in the left precordial leads, indicating that the precordial QRS complexes reflect only massive enlargement of the right ventricle. None of the 23 patients with electrocardiograms described by Sinha et al.[7] had left precordial Q waves. Right axis deviation is almost always present but may not exceed that found in the normal newborn. Right atrial hypertrophy may be prominent.

Correlation with hemodynamic findings: Although we believe that the diagnosis can be established accurately in most of the cases by the clinical criteria cited, cardiac catheterization and angiocardiography may be required for absolute diagnosis since other cardiac anomalies in terminal stages, some amenable to later surgical correction, may present clinical findings that are similar in some respects. Cardiac catheterization may be further useful for prognostic considerations. Findings of low levels of oxygen saturation, pulmonary to systemic flow ratio less than 1 (indicating a high level of pulmonary vascular resistance) and increased pulmonary arterial and, hence, aortic pressures were obtained in patients surviving for more than 7 days. These findings contrasted with those of infants who lived less than 7 days, indicating that a positive correlation can be made between the clinical and hemodynamic findings. This may allow selection for palliative surgical procedures.

Surgical Treatment

To date, all measures have failed in the treatment of patients with hypoplastic left heart syndrome, with death usually occurring in early life. Medical management is rarely if ever adequate, and the surgical results are presently dismal. The main difficulty is that these infants have an abnormality that is incapable of maintaining an adequate systemic circulation. To accomplish systemic perfusion, banding of the right and left pulmonary arteries has been suggested, thus elevating the level of main pulmonary arterial pressure and as-

suring continuance of the right to left shunt by way of the ductus arteriosus.[24]

Creation of atrial septal defect: Some authors believe that a longer survival time is associated with a large atrial septal defect,[24,25] although others[7] found small atrial septal defects associated with prolonged survival time as was seen in 2 of our longer survivors. It has been reasoned that the creation of an atrial septal defect may benefit patients with hypoplastic left heart syndrome by increasing the availability of oxygenated blood to the systemic circulation, and the procedure has been advised in cases where a definite gradient exists between the left and the right atrium.[16] However, surgical creation of an atrial septal defect is difficult because the left atrium and interatrial septum are usually diminutive.[17] In addition, it might be hypothesized that the atrial septal defect might act to diminish the pulmonary venous pressure and further reduce pulmonary vascular resistance, consequently decreasing the necessary right to left shunt at the ductal level. We consider that the creation of a surgical atrial septal defect combined with banding of the pulmonary arteries distal to the ductus arteriosus appears to offer the best chance for survival.

Creation of an atrial septal defect with the Rashkind procedure[26] appears rarely feasible since the left atrium is usually prohibitively small and the inflation of the balloon alone might result in rupture of the atrium, or the maneuver involved in traversing the tiny foramen ovale with the balloon might result in detachment of the left atrium from the left pulmonary veins. Before this procedure is performed, it would appear advisable to determine left atrial size angiographically.

The creation of an ascending aorta to right pulmonary artery shunt concomitantly with the banding of right and left pulmonary arteries has been recently reported in a patient with aortic stenosis and ductus arteriosus.[27] Our data suggest that the creation of such a shunt in infants with hypoplastic left heart syndrome would be not only unnecessary but of no real benefit since spontaneous closure of the ductus arteriosus appears unlikely.

Conclusions

1. Hypoplastic left heart syndrome is described as an entity invariably associated with aortic or mitral valvular atresia, or both, with normally related great vessels and intact ventricular septum.

2. There are 2 clinical groups of patients. The diagnosis in group I can be established in an infant with cardiorespiratory distress combined with feeble or absent pulses in the presence of a hyperactive precordium. The diagnosis in patients of group II is more difficult because they have fair to good peripheral pulses and may be older when first seen, often making hemodynamic study necessary.

3. Electrocardiographic findings of right axis deviation, right ventricular hypertrophy and the uniform absence of Q waves in the left precordial leads are important criteria for the clinical diagnosis in both groups.

4. Radiographic evidence of cardiomegaly and increased pulmonary vascular markings are constant findings. The absence of the ascending aorta in the right cardiovascular silhouette may be helpful in the radiographic diagnosis.

5. The hemodynamic findings indicate that the onset of symptoms and death are most closely related to the imbalance of systemic and pulmonary vascular resistances.

6. The prognosis is virtually hopeless at present, and palliation may be accomplished by surgical creation of an atrial septal defect concomitant with pulmonary arterial banding distal to the patent ductus arteriosus.

7. The patients in group I do not appear to be good candidates for surgical palliation because of the rapid development of a moribund state shortly after birth. In contrast, the patients in group II are not as ill at the time of presentation and are better candidates for surgical palliation if the diagnosis is made promptly.

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Dynamics of Potassium Flux in Cardiac Arrhythmias

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A considerable net myocardial potassium loss was demonstrated in the dog during rapid ventricular tachycardias. This net potassium loss was associated with some serious arrhythmias which invariably induced resistant ventricular fibrillation. The myocardial potassium loss was associated with an increased myocardial oxygen consumption and lactic acid production. These studies suggest that restoration of the myocardial potassium balance may provide a more proper rationale for the treatment of cardiac arrhythmias.

It has been recognized that potassium plays a vital role in cardiac function since Blake[1] in 1839 demonstrated that he could kill animals within seconds after the injection of potassium carbonate, and Ringer[2] 44 years later noted that a potassium infusion could cause failure of the heartbeat. Langendorff[3] recognized that potassium could cause cardiac inhibition in diastole in 1895, but it was not until 1956 that this principle was applied by Effler et al.[4] to arrest the heart during cardiac surgery.[4] Net potassium loss from the myocardium was first reported by Harris et al.[5] in 1954 when they sampled the coronary sinus blood following coronary artery occlusion,[5] and this was confirmed by other investigators.[6–11] These workers believed that the large potassium efflux from the ischemic area was the cause of the supervening ventricular fibrillation. However, the recent studies of Wexler and Patt[12] indicate that the relationship of intracellular potassium balance and arrhythmias might be a more complicated matter, for ventricular fibrillation did not develop in those animals with the greatest potassium efflux. Because of these contradictions and the reports of other investigators,[5,8–11] who intimate that the arrhythmias do not cause myocardial potassium efflux, we devised a series of experiments to establish the possible relationship of arrhythmias and myocardial potassium balance.

Methods and Procedures

Eighteen mongrel dogs of both sexes, weighing from 22 to 25 kg, were anesthetized after an overnight fast with morphine sulfate, 2 mg/kg body weight intramuscularly, followed 30 minutes later by intravenous administration of sodium pentobarbital, 15 mg/kg. Aortic pressure was measured with a catheter inserted into the aorta before opening the chest. While the dogs were maintained by a Harvard artificial respirator on positive pressure ventilation, thoracotomy was performed for installation of test instruments and for application of tincture of aconite to the myocardium. A four side-hole coronary catheter (U. S. Catheter and Instrument Corp., Glen Falls, N. Y.) was introduced 2 cm into the coronary sinus by way of the right jugular vein, and another into the aorta for sampling of blood. A modified short Lehman ventriculography 6F catheter with tapered tip shortened to 1.5 cm was

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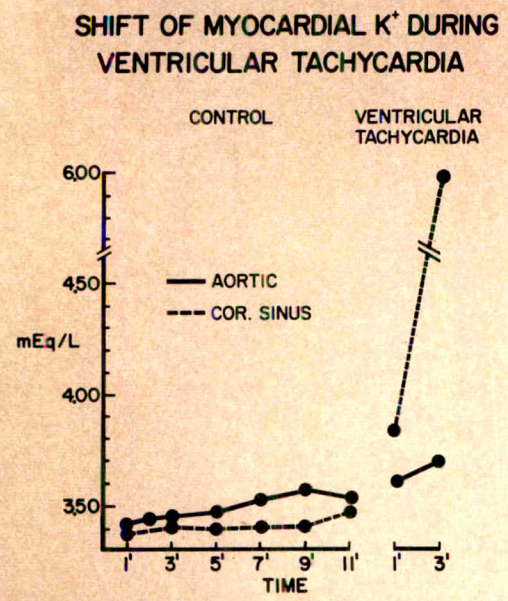

Figure 1. Plasma potassium level in the aorta and coronary sinus remains constant during an 11 minute control period with sinus rhythm. A period of only 3 minutes of ventricular tachycardia results in a myocardial potassium egress of more than 2 mEq/liter (from 3.45 to 5.9).

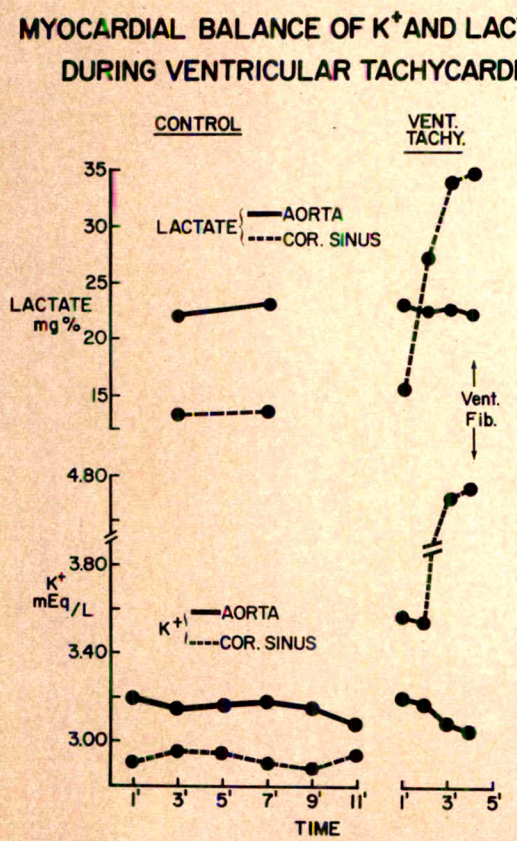

Figure 2. Graph illustrates myocardial potassium egress associated with negative lactate balance during a paroxysm of ventricular tachycardia. Levels of aortic and coronary sinus lactate (**top**) and potassium (**bottom**) are constant during sinus rhythm control period, but during ventricular tachycardia there is a net loss of myocardial potassium associated with production of lactate.

inserted through the left atrium for measurement of left ventricular pressure. A standard lead II electrocardiogram was monitored throughout the experiments. Blood and fluid loss was replaced during surgery by fresh donor dog's blood or normal saline solution administered at a rate of 2 to 5 cc/min. No blood was administered during the remaining procedures.

Measurement of plasma potassium and sodium was performed on an IL-143 flame photometer. The accuracy of this model is less than ±0.5 mEq/liter for serum sodium and ±0.05 mEq/liter for potassium. Samples with any significant hemolysis were discarded. Blood hematocrit was determined from a calibrated microhematocrit tube with an Adams Readacrit centrifuge (Clay-Adams, Inc., New York). Blood pH, pO_2 and pCO_2 were measured on a Beckman physiologic gas analyzer, model 160, at 37C.

Oxygen saturation was determined by using a nomogram[13] with the measured pO_2, pH and temperature. Oxygen content was computed from the oxygen saturation and oxygen carrying capacity of hemoglobin. Lactate concentration was measured by means of the Hans-Jurgens-Hohorst technique[14] and was expressed as mg/100 ml plasma. An index was used to define the myocardial oxygen and lactate extraction. This index involves the ratio of the arteriovenous difference to the arterial concentration of these metabolites, and is expressed in percent.

After establishing a "steady state," in which pO_2, pCO_2 and pH remained within a normal stable range,

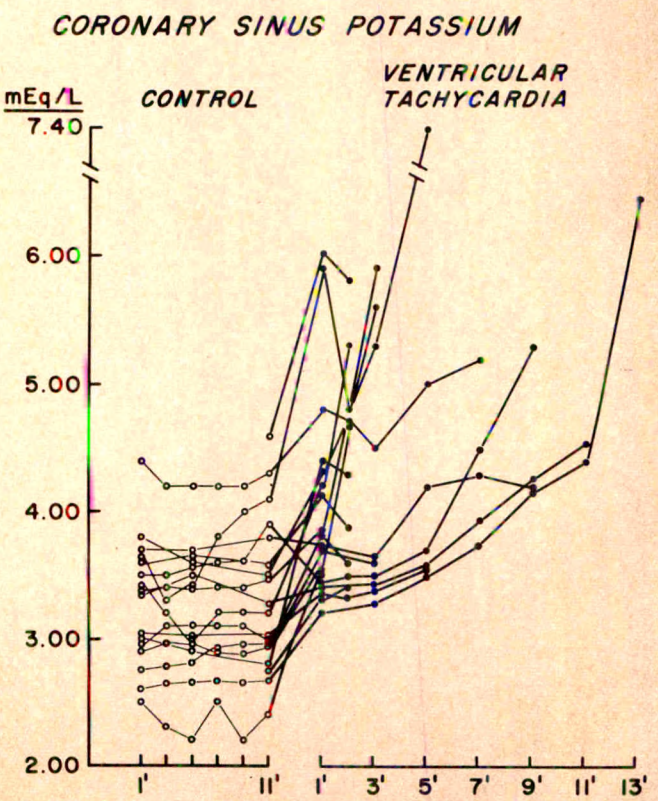

Figure 3. Levels of coronary sinus potassium obtained from each of 18 dogs, during an 11 minute control period and then during ventricular tachycardia. Potassium values remain approximately constant during sinus rhythm and then increase markedly during the tachycardia in all animals.

periodic simultaneous paired sampling of aortic and coronary sinus blood ions was performed at 2-minute intervals for 11 minutes (Fig. 1). Tincture of aconite was then applied to the right epicardial surface of the right ventricle to produce ventricular tachycardia. Ventricular tachycardia usually occurred 2 to 10 minutes after the application of aconite. Plasma potassium and sodium were examined at 1, 2, 3, 5, 7, 9, 11 and 13 minutes after the onset of ventricular tachycardia and after the onset of ventricular fibrillation. Blood hematocrit, pO_2, pCO_2 and pH were also monitored. All data were statistically analyzed by Student's t test, and standard variation was expressed as 1 standard error of mean on each side.

In another series of 6 animals, electromagnetic flow probes were placed around the left anterior descending coronary artery and ascending aorta to measure flow. Simultaneous measurements of aortic and coronary sinus potassium and lactate were also performed in this group (Fig. 2). Data were collected during the stable control period and during the paroxysm of ventricular tachycardia. Student's paired t test was used for statistical analysis for this group.

Results

The concentrations of coronary sinus plasma potassium in 18 dogs are plotted in Figure 3. During the control period of 11 minutes all dogs exhibited relatively stable potassium levels in the coronary sinus, but 1 dog had an increase from 3.60 mEq/liters in the first minute to 4.1 after 11 minutes. This animal exhibited a further abrupt increase in coronary sinus potassium to 5.9 mEq/liters after the onset of ventricular tachycardia.

During ventricular tachycardia, 2 dogs showed an initial decrease in coronary sinus potassium at the start of ventricular tachycardia and then, as ventricular tachycardia persisted, a gradual increase. The remaining 16 dogs exhibited a steep initial increase in coronary sinus potassium as soon as ventricular tachycardia supervened. In 1 dog ventricular tachycardia lasted for only 1 minute; ventricular fibrillation followed, and the animal died. The coronary sinus plasma potassium rose from a low level of 2.40 to 3.50 mEq/liters (Fig. 3). In 7 dogs ventricular fibrillation developed after 2 minutes of ventricular tachycardia, in 3 dogs after 3 minutes, in 2 after 5 minutes, and in 1 after 7 minutes. In the 7 remaining dogs, ventricular tachycardia lasted for 9 minutes in 4 dogs, for 11 minutes in 2 and for 13 minutes in 1. Because of the small number of dogs that survived after 9 minutes of ventricular tachycardia, data after the 9 minute period are not included.

The overall average coronary sinus potassium levels and aortic-coronary sinus potassium differences are listed in Table I and shown graphically in Figures 4 and 5.

The average plasma sodium level was 150.35 (aortic) and 150.46 mEq/liter (coronary sinus) in the control state and 150.06 (aortic) and 149.67 mEq/liter (coronary sinus) during ventricular tachycardia. This represents an arteriovenous difference of 0.29 ± 0.38 and 0.79 ± 0.61, respectively ($P > 0.35$).

In 10 dogs the aortic potassium level remained constant after the induction of tachycardia. The other 8 animals exhibited a rise in the level of aortic potassium from an initial value of 3.68 mEq/liter to 3.86 at 1 minute, 3.78 at 3 minutes, 4.03 at 5 minutes, 3.83 at 7 minutes and 4.00 at 9 minutes. This rise in potassium level was found to

TABLE I

Myocardial Potassium Egress During Tachycardia

	Time of Sampling (min)						
	1	2	3	5	7	9	11
CS K^+ (mEq/liter)							
Control	3.32 ± 0.13*	...	3.14 ± 0.16	3.23 ± 0.12	3.22 ± 0.17	3.22 ± 0.19	3.32 ± 0.14
VT	4.03 ± 0.19	4.31 ± 0.25	4.20 ± 0.32	4.41 ± 0.53	4.34 ± 0.25	4.48 ± 0.27	...
	(18)	(17)	(10)	(7)	(5)	(4)	
P value	<0.01	<0.005†	<0.01	<0.05	<0.005	<0.005	...
Ao-CS K^+ difference (mEq/liter)							
Control	0.09 ± 0.03	...	0.09 ± 0.03	0.11 ± 0.03	0.06 ± 0.03	0.08 ± 0.03	0.09 ± 0.04
VT	−0.43 ± 0.11	−0.69† ± 0.2	−0.49 ± 0.29	−0.47 ± 0.27	−0.35 ± 0.08	−0.48 ± 0.24	...
	(18)	(17)	(10)	(7)	(5)	(4)	
P value	<0.001	<0.005†	>0.05	<0.05	<0.01	<0.05	...

* Standard error of mean.
† Relative to 1 minute control.
Figures in parentheses indicate number of dogs.
Ao = aorta; CS = coronary sinus; VT = ventricular tachycardia.

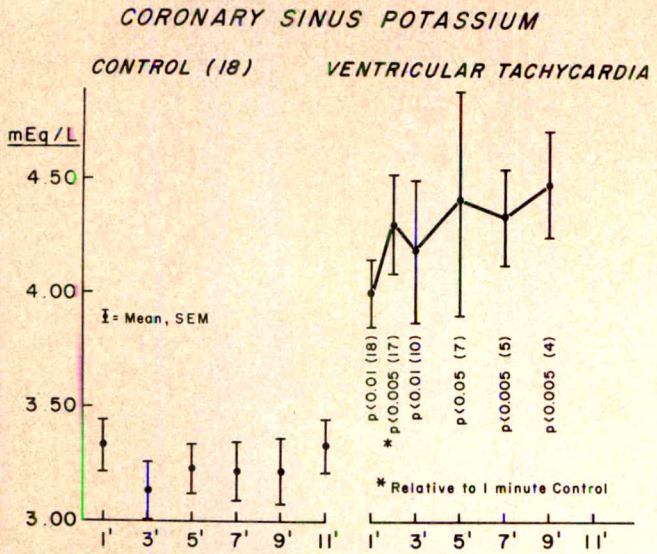

Figure 4. The average coronary sinus plasma potassium remains approximately constant during an 11 minute sinus rhythm control period in 18 dogs, and then rises markedly during ventricular tachycardia.

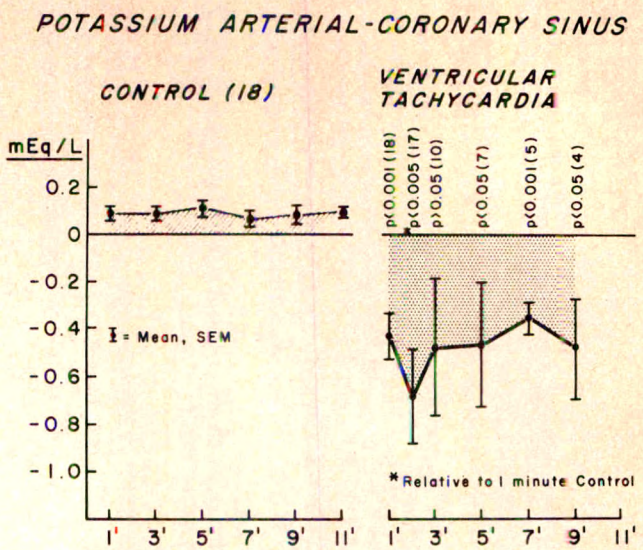

Figure 5. Aortic-coronary sinus potassium difference remains constant during an 11 minute period, but during ventricular tachycardia net myocardial potassium loss reverses this difference.

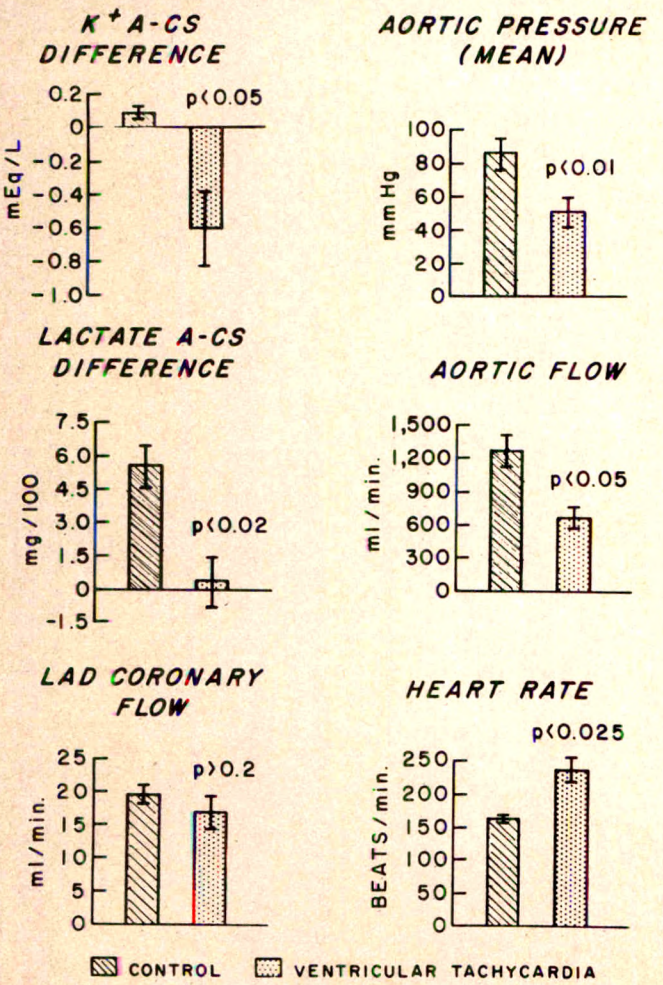

Figure 6. Average hemodynamic and metabolic values are analyzed from 6 dogs during control sinus rhythm and ventricular tachycardia. The net potassium loss from the myocardium during ventricular tachycardia is accompanied by production of myocardial lactate, reduced aortic flow and aortic pressure; flow in the left anterior descending coronary artery decreases slightly.

be statistically nonsignificant relative to the initial value.

In 6 animals flow measurements of the aorta and left anterior descending coronary artery were measured simultaneously with the heart rate, aortic pressure and aortic and coronary sinus potassium and lactate levels (Fig. 6). The overall averages are listed in Table II.

Discussion

Although the episodes of ventricular tachycardia in this study were of short duration, they were always associated with a significant increase in the coronary sinus potassium levels. This myocardial potassium efflux started within 1 minute after onset of the arrhythmia and increased progressively in all animals. The largest increases were from a control level of 3.5 to 7.4 and from 2.6 to 6.5 mEq/liter. Potassium efflux from the myocardium of this magnitude would tend to perpetuate the arrhythmia, making it resistant to therapy, and could lead to fatal ventricular fibrillation. The absolute volume of potassium lost was not calculated because the total coronary sinus flow was not measured. During ventricular tachycardia (Table II) blood flow in the left anterior descending coronary artery decreased only 19 percent, but myocardial oxygen demands were greater than usual. This could explain the simultaneous reduction in lactate extraction or myocardial lactate production. The percent oxygen extraction was increased during ventricular tachycardia when arterial oxygen saturation remained constant.

After the induction of ventricular tachycardia, the arterial potassium concentration increased in 8 of the 18 animals; the average increase was from 0.1 to 0.35 mEq/liter, which is not statistically sig-

nificant. This increase probably represents a leakage of potassium from tissues throughout the body rendered ischemic by the arrhythmia.[15] The arterial-coronary sinus potassium difference would have been larger but for this rise in the arterial potassium level.

During the control period of 11 minutes of sinus rhythm, the difference of the arterial minus coronary sinus potassium remained stable; it averaged 0.1 mEq/liter in the 18 dogs. Tachycardia caused the coronary sinus potassium to increase over the arterial level by an average of 0.5 mEq/liter for a 9 minute period.

We believe that this is the first study to demonstrate a large potassium loss from the myocardium during rapid ventricular tachycardia in the intact heart with normal coronary circulation and innervation. Because it has been suggested that aconite selectively depresses cell membrane permeability to sodium influx,[16] we applied tincture of aconite to the right ventricular surface, close to the right atrium, so that the blood draining that area would not contaminate the coronary sinus blood, which drains about 90 percent of the venous flow from the left ventricle.[17] Thus, our results reflect blood draining only from the left ventricle, not from the region intoxicated by aconite.

TABLE II

Hemodynamics and Metabolism During Tachycardia

	Control (mean ± SEM)	Ventricular Tachycardia (mean ± SEM)	P Value
Heart rate/min	164 ± 3.8	238 ± 18.0	<0.025
Aortic pressure (mean) (mm Hg)	86 ± 11.5	51 ± 9.8	<0.01
Aortic flow (ml/min)	1,241 ± 159.1	646 ± 95.5	<0.05
LAD coronary flow (ml/min)	19.5 ± 3.2	16.9 ± 5.1	>0.2
K^+ (Ao-Cs)(mEq/liter)	0.07 ± 0.03	−0.6 ± 0.23	<0.05
Lactates (Ao-Cs) (mg/100 ml)	5.5 ± 1.00	0.33 ± 1.05	<0.02
Lactates extraction (%)	33.3 ± 1.7	−3.3 ± 6.9	<0.02
Na^+ (Ao-Cs) (mEq/liter)	0.29 ± 0.38	0.79 ± 0.61	>0.35
O_2 saturation (%)			
Ao	95.2 ± 0.4	92.8 ± 2.2	>0.2
Cs	27 ± 4	12.5 ± 3.8	<0.025
O_2 extraction (%)	69 ± 3.7	87 ± 4.4	<0.005
pH			
Ao	7.38 ± 0.022	7.39 ± 0.065	>0.1
Cs	7.34 ± 0.025	7.26 ± 0.065	>0.1

Ao = aortic; CS = coronary sinus; LAD = left anterior descending coronary artery.

Active Ionic Transport Mechanisms

The demonstration of ionic flux of the cations calcium-sodium-potassium across the myocardial cell membrane has shed considerable light on the cause of cardiac arrhythmias and their treatment.[18,19] It is believed that the current required for depolarization of the heart muscle cell is carried by positively charged sodium ions. Upon excitation, the permeability of the cell membrane suddenly changes to allow rapid influx of sodium ions across the sarcolemma and the transverse tubular system. In the interval immediately following this sudden depolarization, sodium influx slows and potassium efflux subsequently supervenes. Depolarization of the cell also triggers the release of ionic calcium and causes it to enter the cell following the sodium influx.[18–20] As calcium influx ceases, potassium efflux increases to rapidly repolarize the cell and allow relaxation. During the period of repolarization, the sodium-calcium pump mechanisms become activated by high energy exchange systems which cause a net loss of sodium and a net gain of potassium. At the same time, calcium has to be stored in the cytoplasmic reticulum, and this is an energy-requiring process.

When potassium is lost from the cell in excessive quantities, the resting potential of the cell decreases toward positivity and reaches a point closer to the threshold for firing. Potassium loss also causes the action potential to shorten, so that the absolute refractory period is reduced, and the nonrefractory period during which the heart muscle cell can be excited is prolonged, so that a small stimulus has greater opportunity to set up an arrhythmia. The shorter the distance between the resting potential and the depolarization threshold, the more irritable the cell. If tachycardia supervenes, we believe that it will cause a further potassium egress, reducing the resting potential nearer the threshold level so that it requires only a small electrical excitation to cause depolarization; in addition, the duration of the action potential will continue to decrease. With still greater potassium loss, the spike of the action potential becomes slowed and of low amplitude. Thus, the excitation process cannot become elicited, the cell becomes inexcitable, and cardiac standstill ensues; these events can give rise to ventricular fibrillation.

Potassium is important for the normal repolarization of the cell and to extend duration of the action potential. A loss of this cation of the kind that occurs after coronary occlusion would set the stage for the induction of an arrhythmia, thus causing a further loss of potassium and tending to perpetuate a more serious arrhythmia. Conversely, it appears that to correct a cardiac arrhythmia potassium must be actively returned across the cell membrane so that normal activation process and action potentials can be resumed.

Reasons for Myocardial Potassium Loss

Because potassium plays such a vital role in the genesis of arrhythmias, it is necessary to consider the causes of potassium loss from the myocardium.

1. Acute cardiac ischemia: Harris et al.[5] first demonstrated that coronary ligation could pro-

duce a net loss of potassium from the heart muscle. Because this was accompanied by arrhythmias, they suggested that potassium released from the ischemic myocardium might act as an excitatory factor at the boundary of the infarction to establish an ectopic focus leading to ventricular tachycardia and fibrillation. However, their figures displayed blood samples taken only at 1 time, that is 7 minutes after coronary occlusion while ventricular tachycardia existed.[5] Our studies might explain why Harris et al. noted a rise in potassium concentration in venous blood drained from the intact myocardium about half as great as that of the vein draining the area of the ischemic myocardium. We believe that ventricular tachycardia in itself accentuated the potassium loss. Our results suggest the net potassium loss was due to increased oxygen demands of the myocardium without a step-up of coronary flow.

Neither Regan et al.[9] nor Cherbakoff et al.[8] noted that ventricular tachyarrhythmias aggravated a further myocardial potassium efflux following coronary occlusion. However, when we reviewed their tracings we noted that a secondary potassium loss in the myocardium often occurred after the onset of the arrhythmia.

Thomas et al.[21] recently demonstrated that after ligation of a coronary artery there was a marked increase in potassium concentration in the local vein draining the area of ischemia which persisted for up to 40 minutes; ectopic arrhythmias and ventricular tachycardias supervened after 20 minutes. Although as much as 20 percent of the myocardium was involved in the ligation, the coronary sinus did not reflect an increase in potassium content. This suggests that the coronary sinus may not always reveal serious potassium egress from localized areas of myocardium.

2. Glycosides: Glycosides can cause a serious intracellular myocardial potassium loss. This was first demonstrated by Calhoun and Harrison[22] in 1931 and confirmed by subsequent investigators.[8,23–28] Several theories have been offered to explain this potassium egress.[28–32] Keynes and Lewis[30] suggested that digitalis attaches itself to a specific site on the external surface of the cell membrane that gives it the ability to inhibit the action of sodium-potassium activated adenosine triphosphatase. Sarnoff et al.[31,32] believed that the acutely induced loss of potassium resulting from the administration of acetylstrophanthidin is related to increased myocardial contractility.

3. Catecholamines plus ischemia: Sarnoff, Gerlings and co-workers[31,33] demonstrated that when norepinephrine was administered to the heart-lung preparation, the coronary sinus potassium diminished, which they regarded as norepinephrine causing an influx of potassium into the heart muscle cell.[31] However, when they first constricted coronary flow and then administered norepinephrine, coronary sinus potassium increased. Their studies suggest that when norepinephrine is administered in the ischemic state it causes a loss of potassium from the heart muscle cell.[33]

4. Increased preload and afterload: In isolated supported heart preparations, when contractility increased there was noted a net loss of potassium from the heart and when contractility decreased, a net gain of potassium.[31,34] The net loss of potassium appeared to vary with the observed increase in oxygen consumption. These investigators believed a causal link existed between increased oxygen utilization and the net loss of potassium.

5. Acidemia: It has been suggested that an overall shift of potassium from the intracellular to the extracellular space, which causes a progressive rise in plasma potassium level, occurs during acute metabolic acidosis and hypercapnia.[35] This might be a primary factor in the causation of cardiac arrhythmias and arrest during and after surgery.[36–38] During the immediate posthypercapnic recovery period, an additional sharp increase in the coronary sinus plasma potassium level accompanied by serious electrocardiographic and arrhythmic disturbances sometimes terminates in ventricular fibrillation or arrest.[39–41]

6. Electrical shock: Childers and Regan and co-workers[42,43] demonstrated an increased coronary sinus potassium concentration immediately after transthoracic electrical discharge, and this net loss continued for up to 10 minutes. They also demonstrated a potassium egress when strophanthidin was administered intravenously in nontoxic doses and subsequent electrical countershock caused still greater loss of potassium extending over a longer period.[43] Cardiac arrhythmias often supervened and persisted for about 7 minutes. It would appear to us upon reviewing their tracings that the arrhythmias might have caused a further increase in the coronary sinus potassium levels. We believe that the arrhythmias that follow countershock are primarily due to potassium egress which disturbs normal resting and action potentials. We often noted that electrical countershock in nondigitalized dogs increased the arterial as well as the coronary sinus potassium concentration.[44] We believe that the reason for the increased arterial potassium is that electrical shock causes a release of potassium from the muscles of the chest wall as well as those of the myocardium itself.

7. Arrhythmias: We have demonstrated that tachycardias caused a significant potassium egress from the intact heart in all 18 experiments and that this event terminated in ventricular fibrillation (Fig. 3). Recent studies by Ebert et al.[45] demonstrated that the potassium content of the atrial muscle was much less in patients with chronic atrial fibrillation than in those with regular sinus rhythm. Parker et al.[46] recently reported that car-

diac pacing at rapid rates was associated with a net myocardial potassium loss and those potassium losses were immediately balanced by myocardial potassium uptake after pacing. Myocardial potassium loss was significantly greater in the group of patients with coronary artery disease and was closely associated with myocardial lactate production and reduction in coronary sinus blood pH.[46] We have also noted a myocardial potassium egress during aconite-induced ventricular tachycardia which was associated with excessive production of myocardial lactate and a reduction of pH in coronary sinus blood (Table II).

Causes of Potassium Egress During Tachycardia

Several theories have been proposed to account for the potassium efflux when the cardiac rate is increased.

1. Increased contractile state: Gilmore and coworkers[31,34,47] noted when contractility increased, there was a net loss of potassium from the heart and when contractility decreased there was a net gain of potassium. The amount of the net loss of potassium appeared to vary with the observed increase in oxygen consumption. An abrupt increase in heart rate also increases the total period of contraction and, thus, the requirements of the contractile elements for energy utilization. They postulated that a causal link between the observed net loss of potassium and the increased contractile state as well as oxygen utilization is based on an increased metabolic activity. Clancy[48] and Brown and Goott[49] demonstrated that an increase in myocardial metabolic activity, which is accompanied by increased production of carbon dioxide and hydrogen ion concentration, will cause an increase in the ratio of H_i^+/H_e^+ (where H_i^+ is the intracellular hydrogen ion concentration and H_e^+ is the extracellular hydrogen ion concentration) and thus promote a net loss of potassium from the cell.

2. Less time for potassium reentry: Hadju[50] demonstrated that since a net loss of myocardial potassium occurs as a result of the increase in the number of repolarizations, the decrease in interstimulus interval does not permit enough time for potassium reentry. The increased repolarizations cause an increase in myocardial energy requirements which is reflected by a transient diminution in the rate of ion transport at the membrane level. This reduces the inward passage of potassium through the membrane and accounts for a net myocardial potassium loss.

3. Shortened interstimulus interval: Gilmore and Gerlings,[51] using the isolated blood perfused dog heart, determined the influence of changing the interstimulus interval. Doubling the number of contractions while maintaining the number of stimuli constant, or by changing paired pacing to double heart rate, had essentially the same effect on myocardial potassium balance. They concluded that the duration of the interstimulus interval is the principal determinant of myocardial potassium balance. The interstimulus interval is greatly shortened in tachycardias and this could account for the potassium loss.

4. Sodium pump lag: Langer et al.[18–20] postulated that the loss of potassium observed with increasing frequency of contraction is due to a sodium pump lag which allows for a transient net loss of potassium. They have shown that as the rate is increased the adenosine triphosphatase mechanism is stimulated by the net sodium gain inside the cell and this is associated with a potassium loss. Eventually, as the rate speeds up past a certain point, the adenosine triphosphatase mechanism reaches a maximum and a more progressive potassium loss results.[52,53]

5. Squeezing effect of mechanical systole: Sjostrand[54] believed that the cyclic variations of potassium efflux which correlate with the contraction of isolated heart muscle may be due in part to a squeezing effect resulting from mechanical systole. However, this was disproved by the paired pacing experiments of Gilmore and Gerlings,[51] which did not show a net change in myocardial potassium balance when the number of mechanical systoles was doubled.

6. Increased coronary flow: Others explained the potassium loss when the rate speeded up as due to an increased coronary flow causing a washout of potassium. Our and other experiments[50] did not demonstrate an associated increase in coronary flow; therefore, the observed potassium egress could not have been due to a washout effect.

7. Anaerobiasis: Our experiments exhibited the coronary sinus lactic acid increased, suggesting anaerobic conditions existed during the tachycardia which was probably due to the relatively increased oxygen demands during the tachycardia.

Treatment of Tachyarrhythmias Due to Potassium Loss

As a result of our studies we conclude that a basic principle in the treatment of tachyarrhythmias is the inclusion of methods that restore myocardial potassium balance. The latter can best be accomplished by correcting a state of hypoxemia if it exists. Cherbakoff et al.[8] demonstrated that infusion of insulin-glucose or sodium bicarbonate solution, or both, into the coronary artery will reduce the coronary sinus potassium efflux following the coronary ligation, and that the cardiac rhythm will remain regular for a prolonged period of time. Administration of hypertonic glucose and saline solutions may prevent serious electrocardiographic and arrhythmic disturbances during the post-hypercapnic recovery period; this recovery period is accompanied by myocardial potassium egress.[38] Sodi-Pallares et al.[55] have observed that administration of potassium in the

form of polarizing solution (glucose, insulin and potassium chloride) prevents or diminishes the appearance of ectopic beats or rhythms after coronary occlusion in animals and man. Some have reported effective results when polarizing solution is administered to patients with atrial and ventricular tachycardia not related to digitalis administration. Regan et al.[9] noted that when a solution of potassium combined with glucose and insulin (GKI) was administered intravenously, it corrected ischemic arrhythmias because it restored the myocardial potassium loss. However, his later studies intimated the effect on the myocardium was not direct because when GKI solution was injected directly into the coronary artery, digitalis-induced tachycardias were corrected in only 1 of 5 animals.[56] However, it is known that an intracoronary infusion of solutions containing potassium might act as an irritant,[57] and this could explain why the arrhythmias were not always corrected in Regan's experiments.

Both quinidine[31] and beta adrenergic blocking agents[58,59] cause a net gain of myocardial potassium, and this might explain some of their antiarrhythmic action. Helfant et al.[60,61] demonstrated that diphenylhydantoin restored myocardial potassium loss due to digitalis induced arrhythmias in the intact dog's heart, but Miller and Gerlings and co-workers[62,63] later challenged this finding with what would appear to be variable results in the heart-lung preparation using whole blood techniques for measuring potassium. Regan et al.[9] concluded that because procainamide regulated potassium balance it converted strophanthidin-induced arrhythmias. However, we question whether the restoration of myocardial potassium might have resulted from conversion of arrhythmias.

Our studies show that a considerable net myocardial potassium loss occurs during rapid ventricular tachycardias. This is not necessarily associated with a reduction in coronary flow but is accompanied by increasing levels of lactic acid in the coronary sinus, thus indicating myocardial ischemia secondary to excessive myocardial oxygen consumption. The net potassium loss may perpetuate other, more serious arrhythmias and cause them to be resistant to therapy. Further study is required to determine if the concept of restoring myocardial potassium balance may provide a new basis for treatment of arrhythmias.

Acknowledgment

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Treatment of Supraventricular Tachycardias by Right Atrial Alternating Current Stimulation

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In 6 patients with supraventricular tachycardias, induction of atrial fibrillation by alternating current stimulation of the right atrium was found to be an effective and safe method for terminating these arrhythmias or slowing the ventricular rate. The latter, after induction of atrial fibrillation, provided a good clinical guide for judging the need for further administration of digitalis.

Pharmacologic therapy for supraventricular tachycardias is often unsuccessful, whereas direct current (d-c) countershock in patients receiving digitalis preparations may be hazardous.[1–4] Recent reports[5–17] suggest that various modes of atrial stimulation may be safer than d-c countershock in the management of supraventricular tachycardias during administration of digitalis.[5–7] The purpose of this paper is to report that the application of alternating current (a-c) to the right atrium provides an alternative means of excitation and is useful in the treatment of these arrhythmias.

Materials and Methods

Six patients, aged 16 to 85 years, with supraventricular tachycardia formed the basis for this study, and Table I presents the relevant clinical data pertaining to them. In each case a transvenous bipolar electrode was introduced percutaneously into the right atrium under fluoroscopic control. Alternating current was then applied to the atrium by a Cordis a-c stimulator. Before and immediately after a-c stimulation, bipolar atrial electrograms were recorded concomitantly with a standard lead electrocardiogram in order to document the rhythm. The method used in these procedures has been described elsewhere.[5,6] All records were obtained on a multichannel photographic recorder. A battery-powered alternating current stimulator able to deliver currents of 40 to 1,000 Hz at 1 to 12 milliamperes was used, but the actual current delivered to the right atrium was 60 or 80 Hz at 2 to 6 milliamperes with a stimulus duration of 2 to 4 seconds.

Results

Of the 6 patients studied, 2 presented with an atrioventricular (A–V) junctional tachycardia (Fig. 1 and 2) and 4 with atrial flutter (Fig. 3 to 5). In each instance a-c stimulation immediately converted the rhythm to atrial fibrillation (Table I).

In Case 1 (Fig. 1) atrial fibrillation persisted for approximately an hour before reverting spontaneously to sinus rhythm. In Cases 2 and 3 the fibrillation continued for only a few minutes and then reverted to normal sinus rhythm. In Case 2 (Fig. 3), the cessation of atrial fibrillation was followed by several A–V junctional beats, but finally a stable sinus rhythm ensued. In the remaining 3 subjects the induced atrial fibrillation changed of its own accord to atrial flutter. In Patients 4 and 5 (Fig. 2 and 4) the fibrillation

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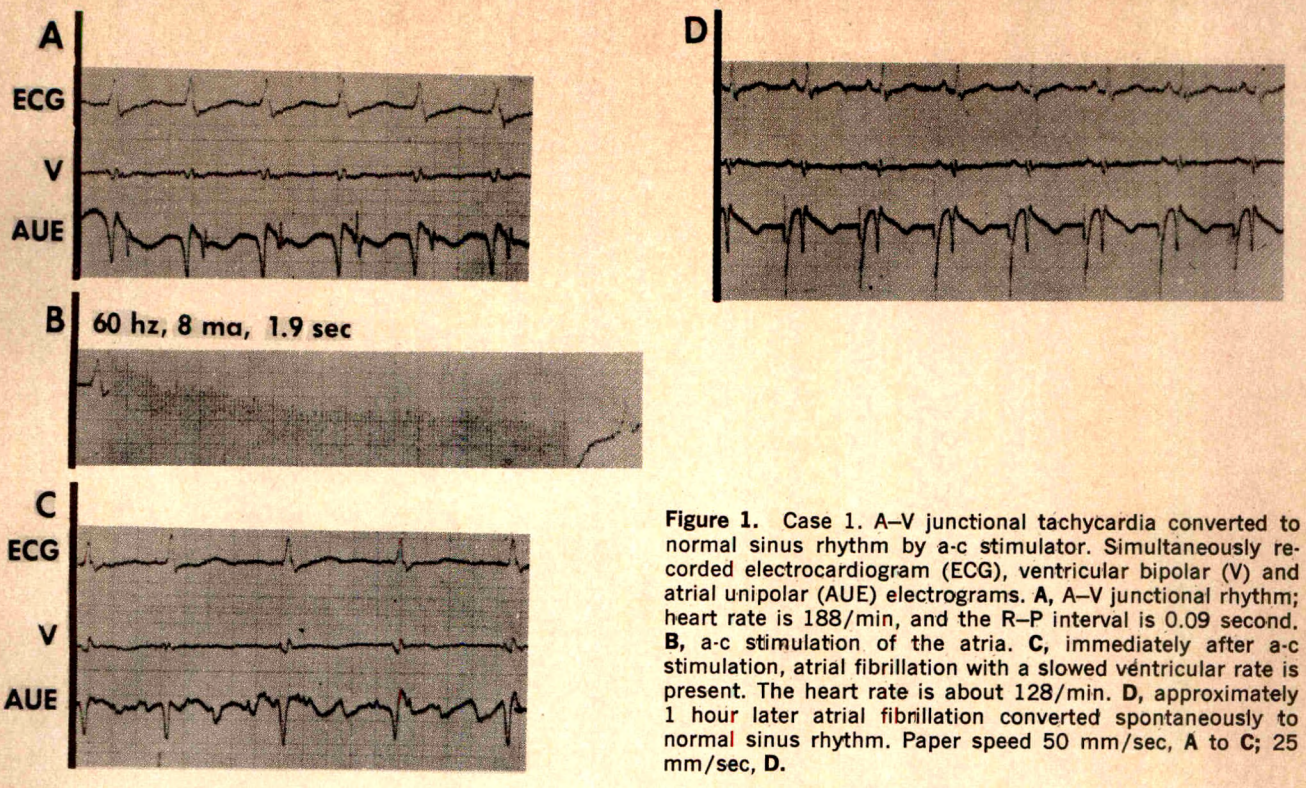

Figure 1. Case 1. A–V junctional tachycardia converted to normal sinus rhythm by a-c stimulator. Simultaneously recorded electrocardiogram (ECG), ventricular bipolar (V) and atrial unipolar (AUE) electrograms. **A,** A–V junctional rhythm; heart rate is 188/min, and the R–P interval is 0.09 second. **B,** a-c stimulation of the atria. **C,** immediately after a-c stimulation, atrial fibrillation with a slowed ventricular rate is present. The heart rate is about 128/min. **D,** approximately 1 hour later atrial fibrillation converted spontaneously to normal sinus rhythm. Paper speed 50 mm/sec, **A** to **C;** 25 mm/sec, **D.**

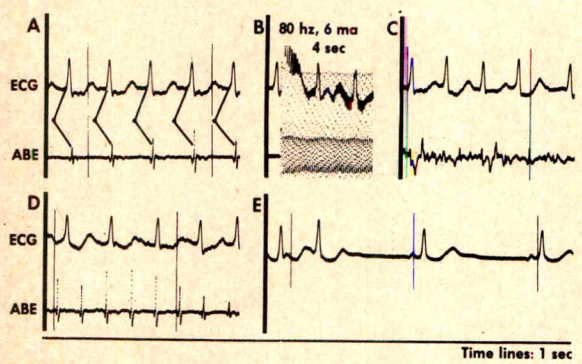

Figure 2. Case 4. A–V junctional tachycardia converted to normal sinus rhythm by a-c stimulation. Panels **A, C** and **D,** simultaneous standard-lead electrocardiogram and atrial bipolar electrogram. **A,** A–V junctional tachycardia with 1:1 retrograde activation of the atria. The heart rate is 180/min. **B,** a-c stimulation of the atria. **C,** immediately after atrial stimulation, atrial fibrillation with a rapid ventricular response is present. **D,** approximately 5 minutes later, atrial fibrillation changed spontaneously to atrial flutter with 2:1 A–V block. **E,** a-c stimulation was repeated and atrial fibrillation was again induced. About 1½ minutes after the cessation of a-c stimulation, spontaneous termination of atrial fibrillation and reversion to normal sinus rhythm occurred.

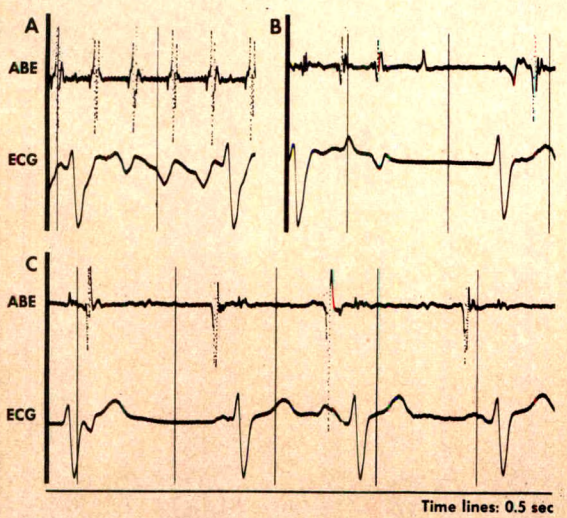

Figure 3. Case 2. Conversion of atrial flutter to normal sinus rhythm by a-c stimulation. **A,** atrial flutter with 4:1 A–V block. **B,** approximately 2 minutes after a-c stimulation, atrial fibrillation spontaneously terminates. The beat following cessation of atrial fibrillation is an A–V junctional beat with retrograde atrial activation. **C,** the first 2 beats are A–V junctional beats, the first of which is associated with retrograde atrial activation, and the second of which is A–V dissociated and is preceded by a normally conducted sinoatrial beat. After the second beat the rhythm stabilizes to normal sinus.

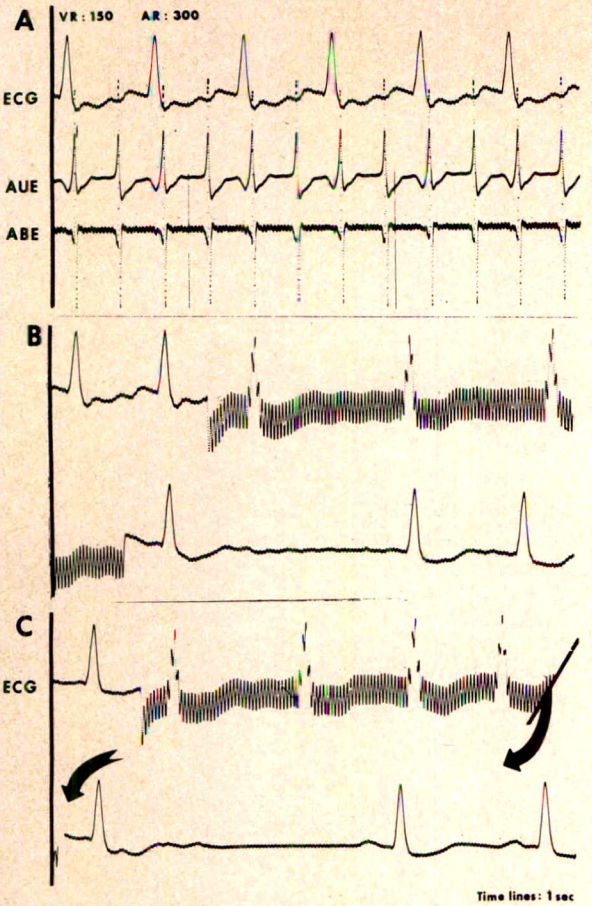

Figure 4. Case 5. Atrial flutter converted to normal sinus rhythm by a-c stimulation. **A,** simultaneous electrocardiogram, atrial unipolar and atrial bipolar electrograms. The atrial rate (AR) is 300/min, and the ventricular rate (VR) is 150/min. Atrial flutter with 2:1 A–V block is present. **B,** atrial a-c stimulation induces atrial fibrillation, and the ventricular rate was slowed. **C,** continuous electrocardiogram. There was a recurrence of atrial flutter. Reapplication of a-c stimulation of the atria converted the rhythm to normal sinus.

was induced a second time with a subsequent change, again spontaneously, to normal sinus rhythm.

In Case 6, the patient had received 0.8 mg of Cedilanid and 1.0 mg of digoxin during the 36 hours before the attempted a-c conversion. The latter immediately altered the rhythm from atrial tachycardia with a ventricular rate of 130/min to a more rapid atrial dysrhythmia with a ventricular rate of approximately 60/min and occasional premature ventricular beats (Fig. 5). After 15 minutes the rhythm again reverted to the original atrial tachycardia. The slow ventricular rate with occasional ventricular premature beats, after stimulation, suggested that the patient had received at least a full therapeutic dose of digitalis. It was therefore decided not to make further attempts to achieve normal sinus rhythm by atrial stimulation or d-c countershock. Approximately 24 hours later the rhythm changed spontaneously to atrial fibril-

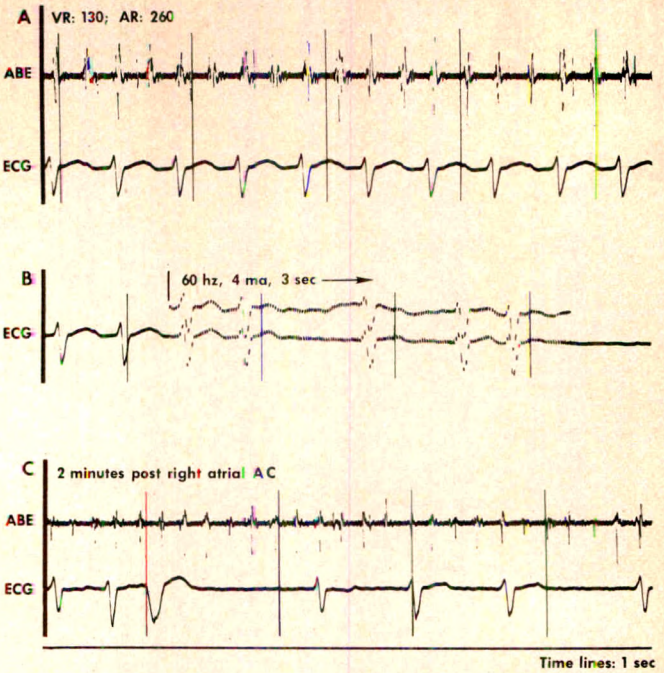

Figure 5. Case 6. Slowing of the ventricular rate by a-c stimulation. **A,** atrial flutter with 2:1 A–V block. **B,** right atrial a-c stimulation with immediate slowing of the ventricular rate. **C,** the a-c stimulation altered the supraventricular dysrhythmia; the atrial rate is increased and the ventricular rate decreased. Associated with the slowing of the ventricular rate there are occasional premature ventricular beats (see text).

TABLE I

Clinical Information in 6 Cases

Case no.	Age (yr)	Disease	Medications	Before a-c	After a-c
1	40	Bowel obst. 1 day postop.	None	AV–JT	A Fib → NSR
2	85	ASHD	Dig.	A Fl	A Fib → NSR
3	16	History of syncope, prolonged Q-T interval	None	A Fl	A Fib → NSR
4	68	ASHD	Dig., quin.	AV–JT	A Fib → A Fl
				A Fl	A Fib → NSR
5	45	Hypertension	Dig.	A Fl	A Fib → A Fl
				A Fl	A Fib → NSR
6	67	ASHD	Ced., + dig.	A Fl	A Fib → A Fl

a-c = alternating current stimulation; A Fib = atrial fibrillation; A Fl = atrial flutter; ASHD = arteriosclerotic heart disease; AV–JT = A–V junctional tachycardia; ced. + dig. = cedilanid, 0.8 mg, + digoxin, 1 mg, in previous 36 hours; dig. = digoxin; NSR = normal sinus rhythm; quin. = quinidine; obst. = obstruction; postop. = postoperatively.

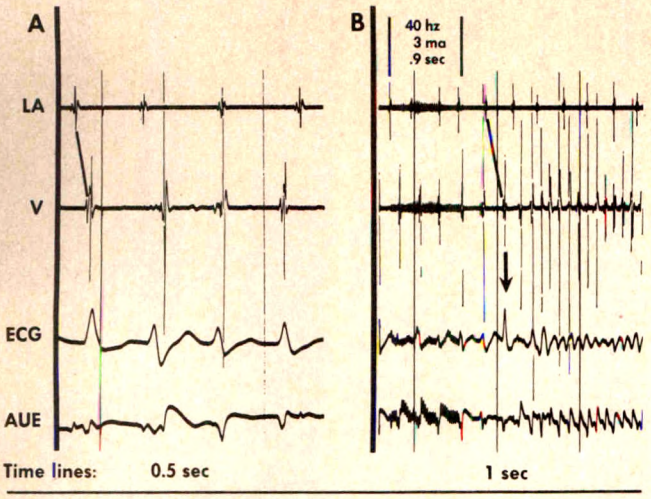

Figure 6. Canine experiment: The initiation of ventricular fibrillation by a supraventricular beat during overt digitalis toxicity. **A**, control. Sinus rhythm alternating with ventricular tachycardia; A–V dissociation is present. The first beat is a sinus beat, and the second a fusion beat. **B**, a-c stimulation during digitalis-induced ventricular tachycardia with A–V dissociation elicited premature atrial beats. One of the premature atrial beats was normally conducted to the ventricles during the ventricular vulnerable period and induced ventricular fibrillation. (Supraventricular QRS configuration was established by previous recordings.) LA = left atrial electrogram (bipolar); V = ventricular electrogram (bipolar).

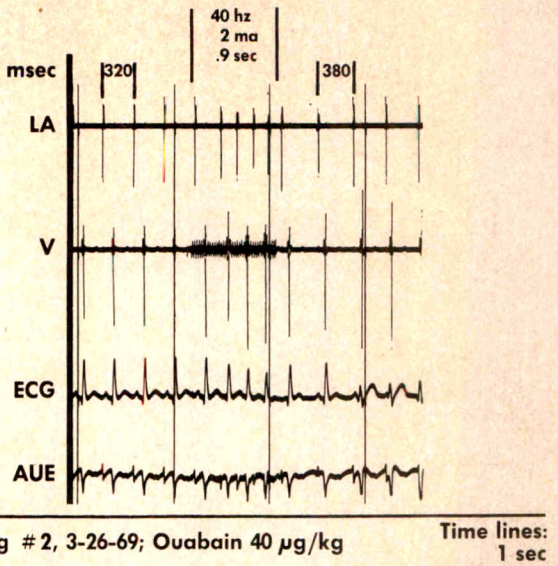

Figure 7. Canine experiment: The unmasking of digitalis toxicity by a-c stimulation of the atria following administration of 40 μg/kg of ouabain. In this experiment 50 μg ouabain produced overt digitalis toxicity. The P–P interval during normal sinus rhythm was 320 msec. a-c stimulation resulted in a short run of multifocal atrial tachycardia. After cessation of a-c stimulation, there was spontaneous reversion to sinus rhythm. The first P–P interval after reversion was prolonged to 380 msec. This slowing of the heart rate permitted the escape of a digitalis-accelerated ventricular pacemaker.

lation and after a further 90 minutes to normal sinus rhythm.

Discussion

The successful use of various modes of electrical stimulation of atria for the treatment of supraventricular tachycardias has been recorded by other investigators.[5–17] Thus, paired and coupled pacing of the atria are known to slow the ventricular rate during sinus tachycardia[8] and low frequency a-c stimulation has been reported to lessen the ventricular rate in supraventricular tachycardias.[9] Termination of reciprocal tachycardias by pairs of atrial stimuli,[10–12] as well as an atrial tachycardia by a single stimulus,[13] has also been described. Atrial tachycardias, atrial flutter and A–V junctional tachycardias have been treated successfully by rapid atrial stimulation (200 to 1,200 pacemaker impulses/min.).[5–7,15–17]

Previous experience with rapid atrial stimulation has shown that electrical induction of atrial fibrillation is an effective and safe method for treating patients with supraventricular tachycardias who are receiving digitalis.[5–7] Therefore, it seemed worthwhile to study the clinical applicability of inducing atrial fibrillation by a-c stimulation of the right atrium in patients with such tachycardias.

Experimental testing for safety: Before attempting the procedure clinically, safety was tested in 10 experiments on dogs. These comprised right atrial stimulation with alternating current before and after the animals were given toxic doses of digitalis—intoxication being assumed when spontaneous ventricular tachycardia occurred. In 1 dog, shortly after the a-c stimulation had been applied, a supraventricular beat interrupted a digitalis-induced ventricular tachycardia. This occurred during the vulnerable period of a cardiac cycle and caused ventricular fibrillation (Fig. 6). Figure 7 shows the unmasking of digitalis toxicity by right atrial a-c stimulation. The ventricular rate was slowed, thus permitting the escape of a previously hidden digitalis toxic ventricular pacemaker. In these experiments, there was no instance in which a-c stimulation had a direct deleterious effect on ventricular activation. The results of this work clearly demonstrated that right atrial a-c stimulation is a safe method for inducing alterations in atrial rhythm with a succeeding slowing of the ventricular rate. However, the slowing of the ventricles may unmask digitalis toxicity.[5,6]

Clinical application: It is well known that supraventricular tachycardias that revert spontaneously to normal sinus rhythm often pass through an initial interim period of atrial fibrillation. The clinical results of this study, together with the experience of others, confirm that atrial fibrillation is usually a self-terminating dysrhythmia unless advanced disease of the atria is present.[5–7] Hence, the induction of atrial fibrillation by a-c stimulation of the right atrium in patients with supraventricular tachycardias is another mode of atrial stimulation which is therapeutically effective.

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Unidirectional Intraaortic Balloon Pumping in Cardiogenic Shock and Intractable Left Ventricular Failure

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Intraaortic balloon pumping effectively interrupts the vicious circle of cardiogenic shock by increasing coronary blood flow and decreasing left ventricular work and myocardial oxygen requirements. Clinical experience with intraaortic balloon pumping in 4 patients with intractable cardiogenic shock and in 1 patient with intractable left ventricular failure from myocardial infarction is reported. Four of the 5 comatose anuric patients were returned to the coronary care unit alert and in a hemodynamically stable state after an average of 12 hours of pumping.

Since the fate of the patient in cardiogenic shock from myocardial infarction depends upon the balance between myocardial oxygen supply and demand, it is believed that the primary aim of intraaortic balloon pumping should be directed toward increasing coronary blood flow. A dual-chambered balloon mounted on a single lumen catheter is described which, in contrast to the conventional single-chambered balloon, pumps the blood unidirectionally toward the root of the aorta and markedly increases coronary and cerebral blood flow. A safety chamber is interposed between the intraaortic balloon and driving unit, which permits use of carbon dioxide, instead of helium, and a vacuum to assist deflation of the balloon, to assure maximal decrease in left ventricular afterload by facilitating ventricular ejection.

Intraaortic balloon pumping is shown to be an innocuous procedure which is easily instituted at the bedside. A plea is made for earlier referral of patients. Although intraaortic balloon pumping by itself may not salvage these patients with shock, it effectively prepares them for more definitive surgical therapy, such as coronary artery bypass or infarctectomy. One such patient was successfully supported and referred for infarctectomy.

With the introduction of coronary care units and with the prompt treatment of primary cardiac arrhythmias and congestive cardiac failure, the mortality from myocardial infarction has been greatly reduced. However, despite the most meticulous care, in approximately 20 percent of patients with myocardial infarction cardiogenic shock occurs; their condition ultimately becomes refractory to medicinal therapy, and pump failure develops, with a mortality of 80 to 100 percent.[1,2] Since it has not been possible to salvage these patients with medicinal therapy alone, help can come only from a mechanical means of assisting the failing heart. Intraaortic balloon pumping (IABP) at present appears to be the best method because of its simplicity of application and effectiveness in decreasing left ventricular work and increasing coronary blood flow without causing damage to the formed blood elements.[3]

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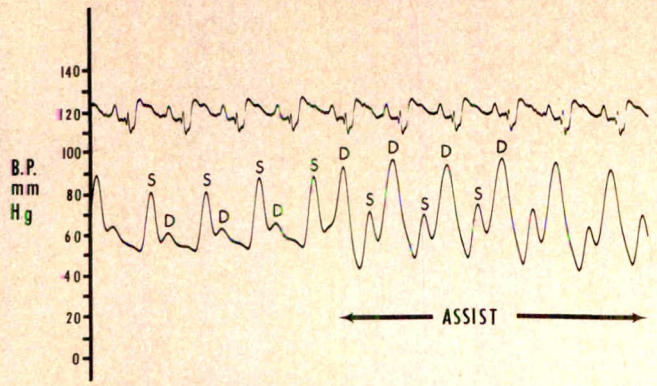

Figure 1. Diastolic augmentation and decrease in left ventricular afterload with initiation of unidirectional intraaortic balloon pumping. Peak systolic (S) pressure decreases approximately 20 mm Hg and diastolic (D) pressure increases approximately 35 mm Hg.

Originally developed by Moulopolos et al.,[4] the feasibility of clinical application has now been well demonstrated.[5–9] However, the commonly employed cylindrically shaped single-chambered or segmental balloons[5,10] displace blood both cranially and peripherally and thereby dissipate much of their effectiveness in augmenting coronary blood flow. The survival of patients from myocardial infarction is ultimately determined by the balance between myocardial oxygen supply and demand.[11] We, therefore, have developed a dual-chambered balloon which, instead of displacing the intraaortic blood in all directions (omnidirectional), pumps it effectively toward the root of the aorta (unidirectional), thus maximally increasing both coronary and cerebral blood flow. The efficacy of our method is illustrated by the rate with which comatose patients with severe cardiogenic shock and left ventricular failure have become alert and their state hemodynamically stable. Although originally devised as a last resort in the hopeless case, intraaortic balloon pumping has in our hands, proved to be a simple and innocuous procedure that should be considered for the many potential recipients of circulatory assistance before they reach a pre-terminal state.

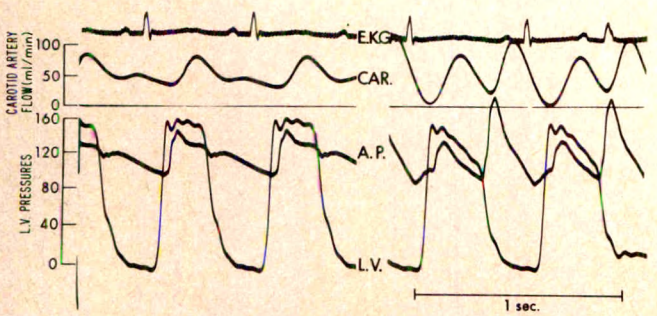

Figure 2. Carotid blood flow (CAR.), aortic blood pressure (A.P.) and left ventricular pressure (L.V.) before (**left**) and during assist (**right**) in canine preparation. Note the large increase in carotid blood flow during diastole and the drop at the end of diastole.

Principles of Intraaortic Balloon Pumping

Intraaortic balloon pumping, like conventional arterioarterial counterpulsation which it has superceded, has 2 objectives: (1) to increase coronary blood flow, and (2) to reduce left ventricular work. If properly timed, inflation of the balloon during diastole will augment diastolic pressure and, hence, coronary perfusion pressure (Fig. 1). Since coronary perfusion is pressure-dependent and occurs mainly in diastole, coronary blood flow will be greatly improved. This effect is greatly enhanced by employing the dual-chambered balloon which, depending on the size of balloon used, pumps up to 35 ml of blood cephalad making it available for coronary and cerebral blood flow. Talpins et al.[3] have demonstrated a 60 to 100 percent increase in coronary blood flow when using the dual-chambered balloon.

Arterial counterpulsation, although it may produce adequate pressure increments in diastolic pressure, is not necessarily associated with movement of blood toward the root of the aorta.[12] Employment of the dual-chambered balloon overcomes this objection by creating a unidirectional flow of blood toward the root of the aorta.

Since deflation of the balloon occurs just before and during systole, aortic impedance is greatly diminished and left ventricular ejection is facilitated. This leads to more efficient left ventricular emptying and, because of the decreased left ventricular afterload, to a marked reduction in systolic pressure, left ventricular work and myocardial oxygen consumption (Fig. 1). In our laboratory studies, left ventricular work was decreased by 28.8 percent and the tension-time index by 35.4 percent.[3]

The improved emptying of the left ventricle has a profound effect on pulmonary hemodynamics and the right side of the heart. Pulmonary edema improves and central venous pressure decreases. This is in keeping with observations reported from our laboratory that the reduction in right ventricular work parallels the decrease seen in the left ventricle.

Timing of inflation and deflation are critical. If inflation occurs too early, the aortic valve will still be open and the pressure wave will coincide with ventricular systole, thereby causing severe embarrassment to the ventricle. On the other hand, if deflation occurs too early in diastole, some blood may be "sucked" into the aorta from the coronary and cerebral circulations, particularly if the aorta is very rigid (Fig. 2).

Technical Aspects

Design and action: Design and action of the dual-chambered balloon are demonstrated in Figure 3. A small spherically shaped "occluding" balloon and a

larger "pumping" balloon are mounted on a single lumen radiopaque catheter. Sequential inflation is obtained by a valve in the catheter. At commencement of diastole, the spherical (distal) balloon is inflated and obstructs peripheral flow in the aorta. This is followed a few milliseconds later by inflation of the pumping balloon. The pumping balloon is 3 to 4 mm smaller in diameter so as to avoid contact with the aortic wall and to permit propulsion of the blood in a cephalad direction, that is, toward the root of the aorta. Both balloons are deflated simultaneously by a vacuum just before and during systole.

The balloons are made of nonthrombogenic urethane of various diameters displacing up to 35 ml of blood. A metallic pellet at the tip assists roentgenographic visualization to ascertain the position of the balloon in the aorta.

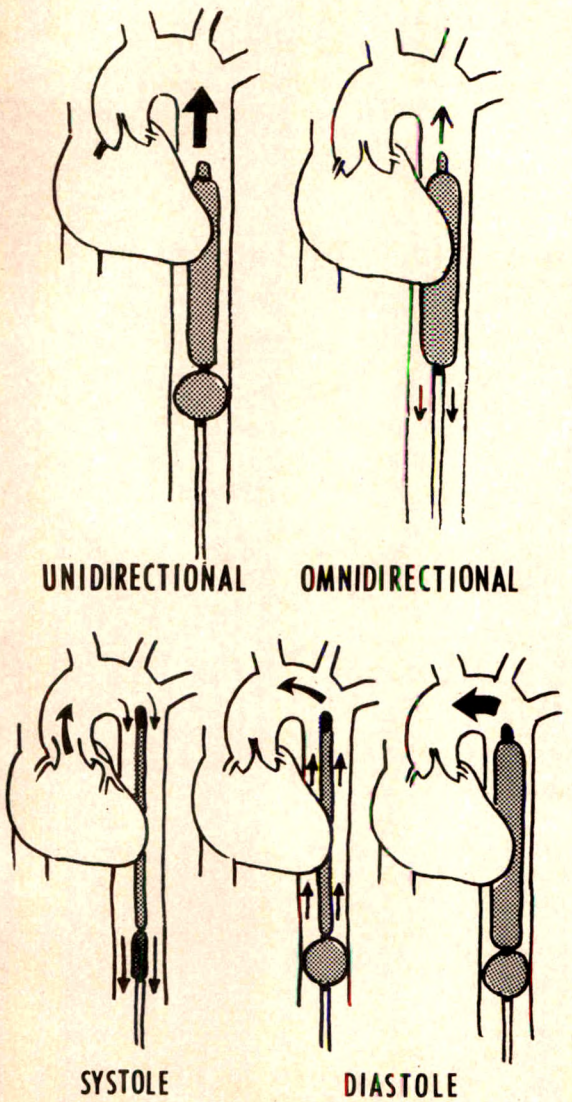

Figure 3. **A,** "unidirectional" pumping of dual chambered balloon versus "omnidirectional" pumping of single chambered balloon. **B,** pumping action of dual-chambered intraaortic balloon. The smaller spherical balloon inflates slightly earlier and obstructs peripheral flow in the aorta. The larger cylindrical balloon then pumps the blood effectively toward the root of the aorta.

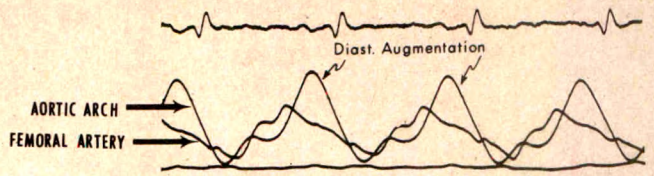

Figure 4. Simultaneous recordings of pressures proximal and distal to dual-chambered intraaortic balloon in patient with cardiogenic shock. Note the diastolic augmentation obtained in the pressure tracing of the aortic arch. There is a small increase in diastolic pressure in the femoral arterial tracing with inflation of the occluding balloon.

Action of the balloon is readily documented by pressure tracings obtained simultaneously during pumping from the aorta and from the femoral artery, that is, both proximal and distal to the balloon (Fig. 4). As can be seen, diastolic pressure is augmented in the aortic arch tracing only. Diastolic augmentation is absent in the femoral artery, indicating that the occluding balloon is effective and that blood is being pumped toward the central aorta only. The small rise in femoral arterial pressure early in diastole is caused by the inflation of the occluding balloon.

With the tip of the balloon at the left subclavian artery, the occluding balloon may be located above the renal arteries and therefore may interfere with renal blood flow during diastole. This was, in fact, the case in 2 of our patients, but urinary flow resumed. However, if urinary flow does not resume, the balloon may be pulled back as soon as the patient is alert and in a hemodynamically stable state so as to occlude the aorta below the renal arteries.

With any balloon some of the blood pumped toward the aortic arch will run off into the subclavian arteries. Neither trauma to the aortic wall nor thrombus formation was observed at autopsy or in any of the animals studied.

Electronic controls: Pumping is triggered by the R wave of the electrocardiogram. We have been using a Datascope control unit which permits employment of an "exhaust-pressure" logic (Fig. 5). In this logic, the R wave triggers deflation of the balloon during the systolic interval. This is followed by inflation during diastole. Thus, the R wave of a premature ventricular contraction will cancel the inflation related to the preceding beat to prevent pump systole from coinciding with ventricular systole. Controls select onset and duration of inflation. The unit can be battery-operated to permit transport of the patient during assistance.

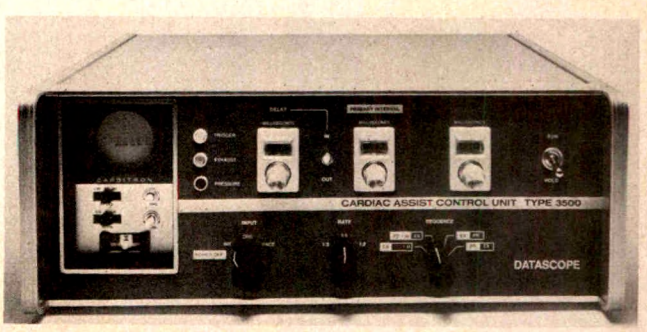

Figure 5. Control panel of the cardiac assist control unit employed in these investigations.

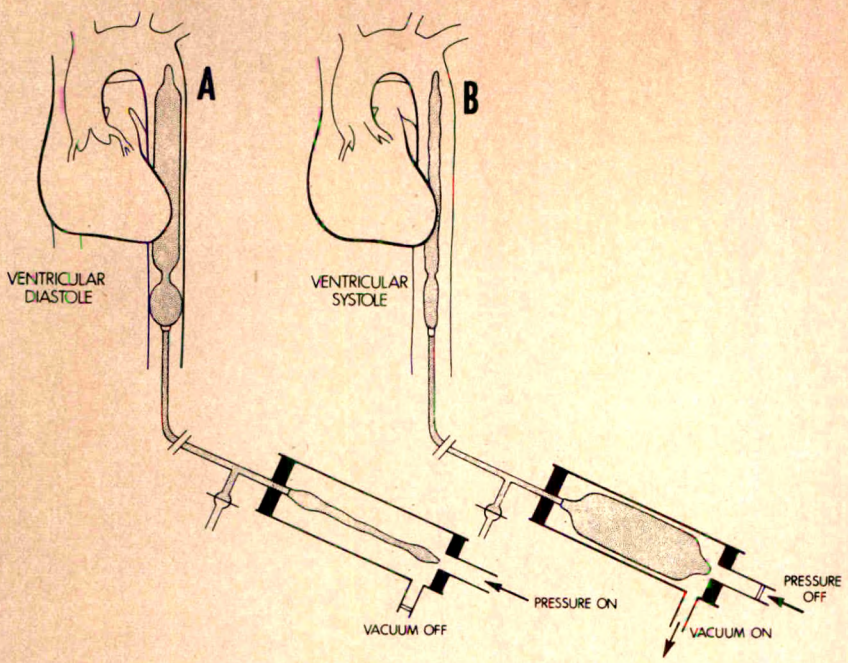

Figure 6. Dual-chambered balloon acting in tandem with slave balloon in the safety chamber. **A,** transfer of gas (CO_2) during diastole from slave balloon to intraaortic balloon. **B,** complete deflation of intraaortic balloon assisted by vacuum acting on slave balloon.

Although the exhaust-pressure logic is the preferred mode of operation and has been employed in all our patients, the electronic system permits the use of a "pressure-exhaust" logic if necessary and also permits the triggering of pumping from the peak systolic pressure in cases in which the electrocardiogram presents difficulty in triggering the electronic circuitry. An additional control permits a gradual increase in the compression of the slave balloon in the safety chamber in order to initiate balloon pumping gradually over many beats and to avoid embarrassing a highly irritable heart (see Fig. 9).

Safety chamber, slave balloon and vacuum: We consider the use of a "safety" chamber interposed between the intraaortic balloon and the pressure valve unit indispensable for clinical work. It makes balloon pumping safe and provides visual control of the action of the intraaortic balloon. The intraaortic balloon is connected by means of a T-piece to an external "slave" balloon contained in a plexiglass chamber (Fig. 6). The chamber is connected to a pneumatic pressure source and vacuum pump which are activated by the electronic control system. This arrangement has the following important advantages:

1. The system is closed. Inflation of the intraaortic balloon is achieved by transfer of gas from the slave balloon to the intraaortic balloon, the volume being predetermined by the capacity of the intraaortic balloon. This causes filling of the intraaortic balloon without distension and possible rupture.
2. The system eliminates the possibility that more gas than the amount introduced into the slave balloon could ever accidentally escape into the aorta.
3. Use of a vacuum acting on the slave balloon assures active and complete collapse of the intraaortic balloon without developing the effects of cavitation.
4. Pressure and vacuum acting on the slave balloon permit rapid gas transfer and the use of soluble carbon dioxide instead of helium.
5. The system provides visual control of the intraaortic balloon's performance by observing inflation and deflation of the slave balloon in the safety chamber.

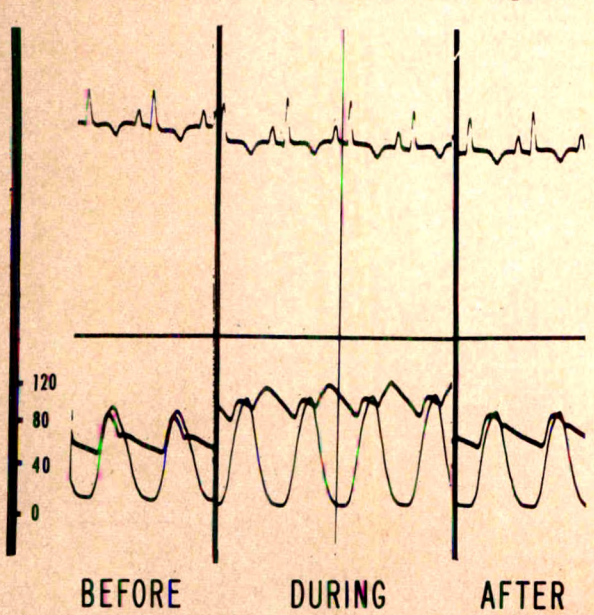

Figure 7. Intraaortic balloon obstructing the aorta. Note increase instead of decrease in ventricular pressure and the poor diastolic augmentation of aortic pressure due to diminished stroke volume of balloon.

The importance of using a vacuum: One of the functions of intraaortic balloon pumping is to reduce left ventricular work. This is accomplished by collapsing the balloon at the end of diastole and at the beginning of systole, thereby decreasing aortic impedance, assisting ventricular ejection and increasing stroke volume. However, intraaortic pressure cannot be relied upon to collapse completely the balloon, particularly with end-diastolic pressures of 30 to 40 mm Hg. The partially collapsed balloon not only may fail to aid ventricular ejection, but may actually produce a hindrance so that left ventricular work is increased rather than decreased. Inflation of a partially collapsed balloon

TABLE I

Clinical Status of 5 Patients

Case no.	Age (yr) & Sex	Previous Infarcts (no.)	Pulmonary Edema		Mental Status		Urinary Output	
			Pre-Assist	30 Min. of Assist	Pre-Assist	30 Min. of Assist	Pre-Assist	Last Hour of Assist
1	63M	1	+++	−	Coma	Alert	Oliguric	38 ml/min (4 hr)
2	76M	0	+++	−	Coma	Alert	Anuric	Anuric
3	64M	1	++	−	Alert	Alert	Anuric	Anuric
4	55F	0	++++	−	Clouded	Alert	Anuric	43 ml/min (11 hr)
5	44M	0	++++	+	Clouded	Alert	Anuric	60 ml/min (14 hr)

will also be less effective since the stroke volume of the balloon will be greatly reduced. The points are illustrated in Figure 7. With balloon pumping, ventricular and aortic pressure increase and diastolic augmentation is minimal. Contrast this with the effects of pumping while employing a vacuum for deflation of the intraaortic balloon (Fig. 1). Whereas Kantrowitz[13] states that use of a vacuum is unnecessary, we believe that use of a vacuum is the single most important factor in assuring maximal decrease in left ventricular afterload by facilitating left ventricular ejection.

Surgical technique: The balloon is inserted under local anesthesia through an arteriotomy in the femoral artery so as to place the tip at the origin of the left subclavian artery. In 3 of our comatose patients, no anesthesia was required. Hemostasis is accomplished by snaring the femoral artery with umbilical tape. Pumping is commenced immediately, and the patient is heparinized. A 10 mm Dacron® prosthesis previously passed over the balloon catheter is then sutured to the femoral artery to permit perfusion of the distal limb during the period of balloon pumping. The snare is then placed around the graft and peripheral circulation is reestablished (Fig. 6).

At this stage a pressure tracing from the femoral artery may be taken. It should record only minimal diastolic augmentation (Fig. 4) early in diastole. The presence of a large diastolic wave in mid-diastole would indicate that the occluding balloon is ineffective and that the diameter of the aorta is larger than initially assumed. In this case, the balloon will simply act as a single-chambered balloon. Pumping can be continued, and at a suitable moment the balloon may be replaced by one of a larger size. Use of a radiolucent bed has greatly facilitated the taking of X-ray films, which are necessary for ascertaining the position of the balloon, monitoring the clearing of pulmonary edema, placing catheters or electrodes, and taking angiograms without disturbing the patient.

Clinical Experience

Selection of patients: Seven patients with cardiogenic shock were studied. The condition of all was refractory to medical treatment; 6 were anuric, and 4 were comatose. In 2 patients with severe aortoiliac disease, the balloon could not be inserted, and the patients died within an hour of the attempts. Twelve other patients met the criteria for mechanical intervention, but all died before assistance could be instituted and, therefore, may be considered control subjects. A strict protocol to exhaust all possibilities of medical therapy was followed in every case, correcting any abnormality in rhythm and insuring that the patient indeed had medically refractory cardiogenic shock. In defining cardiogenic shock, we followed the criteria originally proposed by Binder et al.[14] who listed 5 points for determining its presence and for evaluating the effect of therapy: (1) acute myocardial infarction proved by electrocardiogram; (2) systolic blood pressure of 80 mm Hg or less and pulse rate 110/min or more; (3) clinical signs of peripheral circulatory collapse with marked oliguria or anuria, pallor, cyanosis, or both, sweating, cold skin and dull sensorium; (4) no improvement in the shock state for 30 minutes after relief of pain and administration of oxygen; and (5) absence of ventricular and supraventricular tachycardia, severe congestive heart failure, significant pulmonary infarction, recent cerebrovascular accident, diabetic acidosis, hemorrhage, infection or the effect of hypotensive drugs.

Case material: The 5 assisted patients ranged in age from 44 to 76 years; 4 were male and 1 female (Table I). Two had previously sustained myocardial infarctions. Two were in the group with delayed shock, cardiogenic shock having developed 60 and 38 hours after the onset of infarction, respectively. One additional patient in a terminal state with oliguria and intractable left ventricular failure 2 weeks after myocardial infarction was successfully assisted for 14 hours in preparation for open heart surgery. In the 5 patients the interval from the onset of cardiogenic shock to the initiation of assist averaged 31 hours. Three of the patients had cardiac arrests in the hospital before assistance, 1 having 5 arrests. All patients had pulmonary edema; 2 were stuporous and 2 were in frank coma, thereby reflecting the severe curtailment of cerebral blood flow.

Results

Clinical course: Duration of assistance to hemodynamic stabilization ranged in our patients from between 4 to 16 hours, averaging 12 hours (Table II). The course in Case 4 as well as the changes in the various indexes during the period of assistance are demonstrated in Figure 8. After 11 hours of assistance, the patient's condition was markedly improved, and vasoactive drugs had been discontinued. These changes were typical for the entire group. With the institution of pumping, the need for vasoactive drugs decreased, the pa-

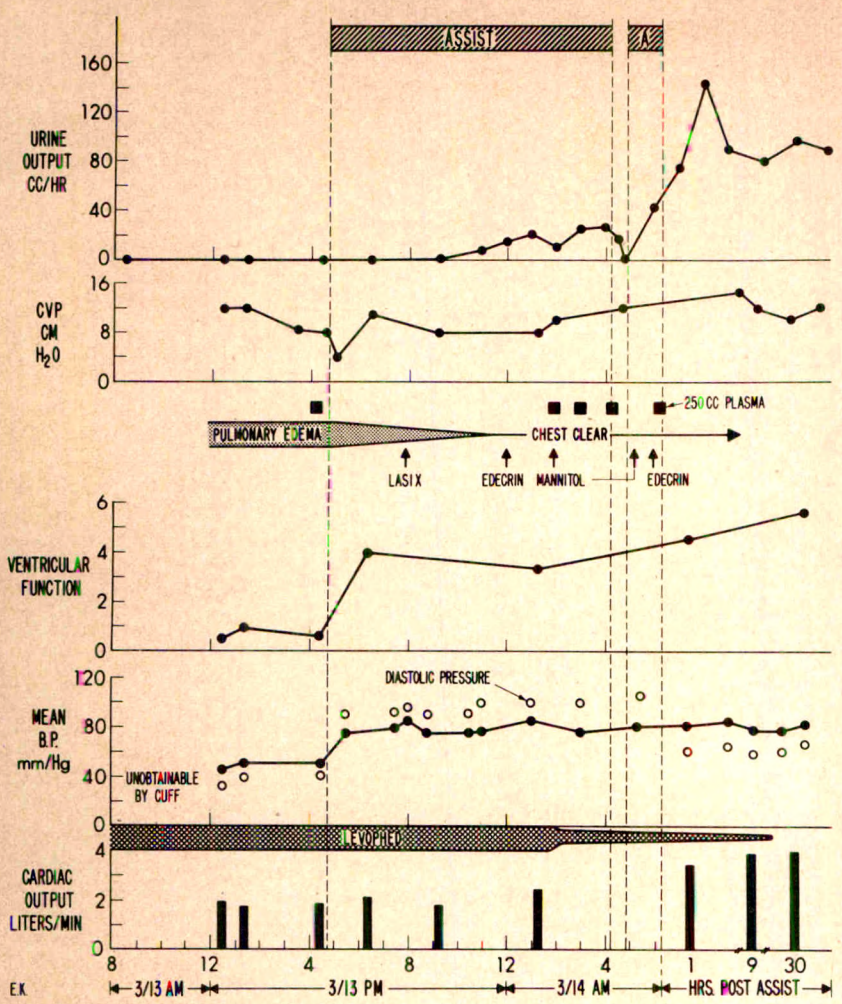

Figure 8. Case 4. Clinical course of patient in cardiogenic shock during intraaortic balloon pumping. Note resumption of normal urinary output during assistance, decrease in central venous pressure with initiation of assist, prompt clearing of pulmonary edema, improvement in ventricular function and decreased requirement of vasopressors during 11 hours of circulatory assistance.

tients responded to diuretic agents, and their myocardia became less irritable. In the first patient, who had 5 separate episodes of ventricular fibrillation at short intervals before assistance, the rhythm became completely regular within a few minutes of assistance. Four patients survived intraaortic balloon pumping and were returned to the coronary care unit. One patient (Case 1) is alive and well 18 months after assistance. A second patient (Case 2), whose condition improved markedly during assistance, died suddenly as a result of extension of the infarct into the septum, acute heart failure and acute atrioventricular dissociation. At autopsy, only approximately 15 percent of myocardium was viable. A third patient (Case 3) remained in a hemodynamically stable state for 2 days after assistance but died of pneumonia and renal failure. He had aspirated while comatose. A fourth patient (Case 4) was well for 7 days after assistance but died suddenly from ventricular rupture and tamponade. The fifth patient (Case 5), with intractable left ventricular failure, had a prompt diuresis with assistance. His pulmonary edema cleared, and cardiac output increased from an initial 3.5 to 5.3 liters/min. After angiographic studies were made, open heart surgery was performed to resect a large left ventricular aneurysm.

Hemodynamic data: Figure 9 illustrates institution of intraaortic balloon pumping in our first patient, who had severe cardiogenic shock with a systolic blood pressure between 30 and 50 mm Hg. Over 30 seconds, the pressure input to the safety chamber was gradually increased until full diastolic augmentation had been achieved. During this period, systolic pressure decreased 15 mm Hg, and peak diastolic pressure gradually increased to 70 mm Hg by the time the intraaortic balloon was completely inflated. In our 4 patients with cardiogenic shock systolic blood pressure before assistance ranged from 40 to 80 mm Hg; with the onset of intraaortic balloon pumping it decreased an average of 11 mm Hg. After 1 minute of assistance, peak diastolic pressure had increased by an average of 54 mm Hg (Table III). Central venous pressure decreased an average of 8 cm of water within the first 30 minutes of assistance; this finding correlates well with the resolution of pulmo-

TABLE II

Clinical Course

Case no.	Interval from Onset of Infarction to Onset of Cardiogenic Shock (hr)	Interval from Onset of Cardiogenic Shock to Initiation of Assist (hr)	Cardiac Arrests (no.)	Duration of Assist (hr)	Course	Cause of Death
1	1	53	5	4	Alive and well 10 months after assist	...
2	60	36	0	16	Improved during assist; died suddenly	Infarct extended into septum; acute heart failure, acute A–V dissociation
3	6	27	1	15	Survived 2 days	Pneumonia, renal failure
4	38	9	1	11	Survived and well for 7 days	Sudden death from ventricular rupture and tamponade
5	*	...	0	14	Improved and transferred for aneurysmectomy	Inadequacy of left ventricular chamber

* Myocardial infarction with intractable left ventricular failure for 2 weeks.

TABLE III

Hemodynamic Data

Case no.	BP Pre-Assist (mm Hg)	Decrease in Systolic BP at Onset of Assist (mm Hg)	Peak Diastolic Pressure—1 Min. of Assist (mm Hg)	Central Venous Pressure (cm H_2O)		Cardiac Index (liters/m^2)		Maximal % Increase in dp/dt During Assist	Free Plasma Hemoglobin at Termination of Assist (mg/100 ml)
				Pre-Assist	30 Min. of Assist	Immediately Before Assist	Post-Assist		
1	80/60	10	102	20	10	1.61	1.83	98.5	7 (4 hr)
2	70/50	10	98	17	8	0.6	0.95	76.3	0.5 (16 hr)
3	50/30	15	90	13	3	0.83	0.93	100.2	...
4	50/35	9	100	8	4	1.06	1.94	79.7	...
5	115/75	25	110	5	4	1.94	2.57	Not computed	0.5 (14 hr)

BP = arterial blood pressure.

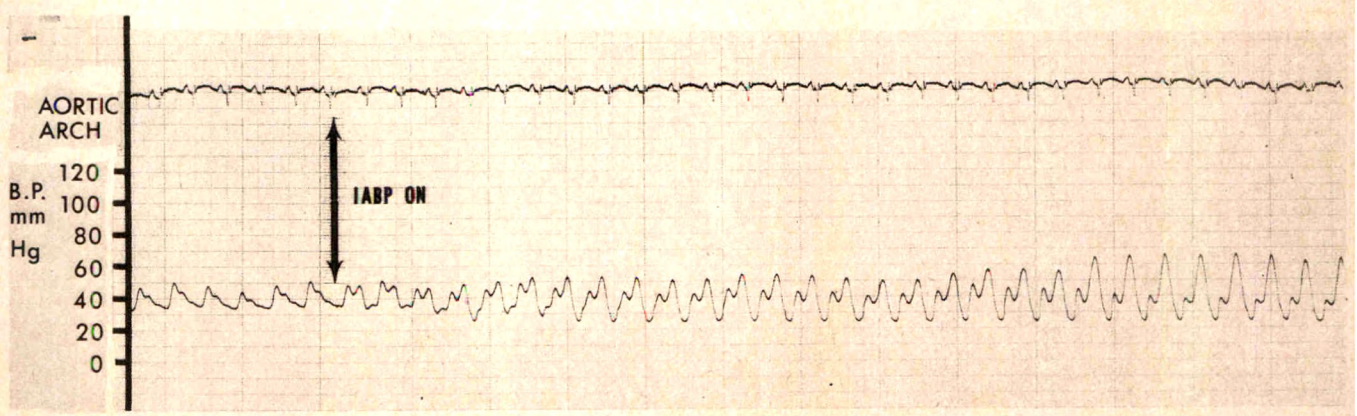

Figure 9. Case 1. Initiation of intraaortic balloon pumping in a patient with severe refractory cardiogenic shock. By gradually increasing the pressure in the safety chamber, a progressive decrease in the systolic pressure is obtained, thus avoiding complications from a highly unstable heart. Full effects of balloon pumping are obtained within 30 seconds.

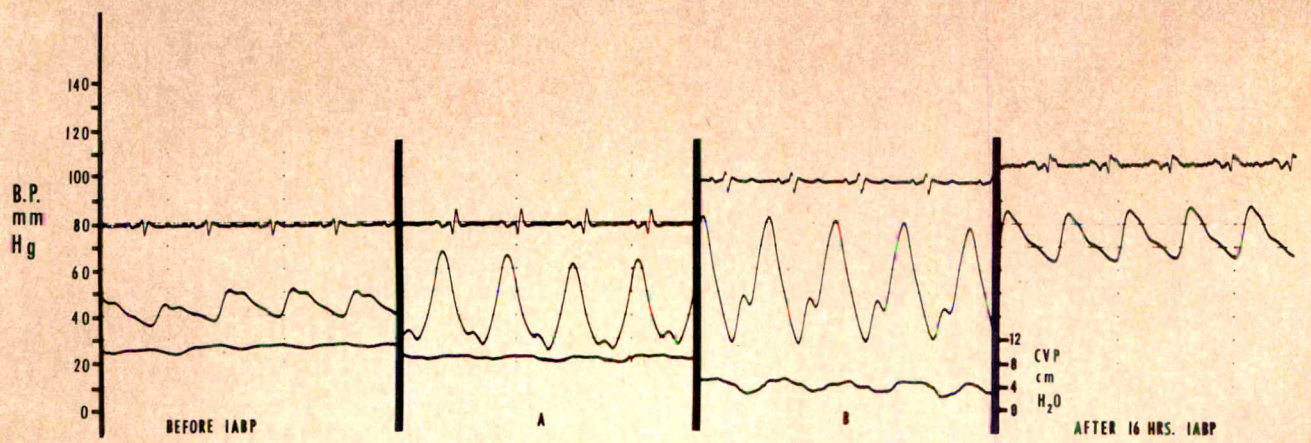

Figure 10. Case 3. Course of blood pressure and venous pressure in patient undergoing dual-chambered intraaortic balloon pumping. Note progressive decrease in central venous pressure and improvement in blood pressure during 16 hours of assistance. **A**, at 1 minute of assistance. **B**, just before termination of assist.

nary edema in these patients (Fig. 10). The rate-corrected presystolic ejection time[15] was reduced an average of 27 percent. The average cardiac index was 1.03 liters/m^2 before assistance and 1.41 immediately after assistance. Although not adequately reflected by the cardiac output, the ventricular function showed marked improvement in all patients. All patients had pulmonary edema before assistance, and within 30 minutes of intraaortic balloon pumping their chests had cleared as shown by both auscultation and roentgenography (Fig. 11). Within 30 minutes of assistance, all patients were alert. Three of the 4 anuric patients had normal urinary output.

Free plasma hemoglobin determinations at the termination of assistance in 3 patients were 7 mg/100 ml (after 4 hours of assistance), 0.5 mg/100 ml (after 16 hours of assistance), and 0.5 mg/100 ml (after 14 hours of assistance), respectively.

Plasma growth hormone levels: Changes in plasma growth hormone and in plasma cortisol levels occur in cardiogenic shock which reflect the clinical state of the patient and correlate well with the hemodynamic changes.[16] In 3 of our patients, both hormones were markedly elevated before intraaortic balloon pumping. Growth hormone levels had risen to between 11 and 19 mμg/ml, and cortisol levels to over 100 μg/100 ml. After a period of pumping when the patients had become alert and were in a hemodynamically improved state, the levels of both hormones dropped markedly.

These changes are well illustrated in Patient 1, whose plasma growth hormone level was 19 mμg/ml before intraaortic balloon pumping was started at a time when he was comatose. After 1 hour of balloon assistance, when he had become alert, the level of growth hormone had dropped to 3.5 mμg/ml. There were no significant changes either in

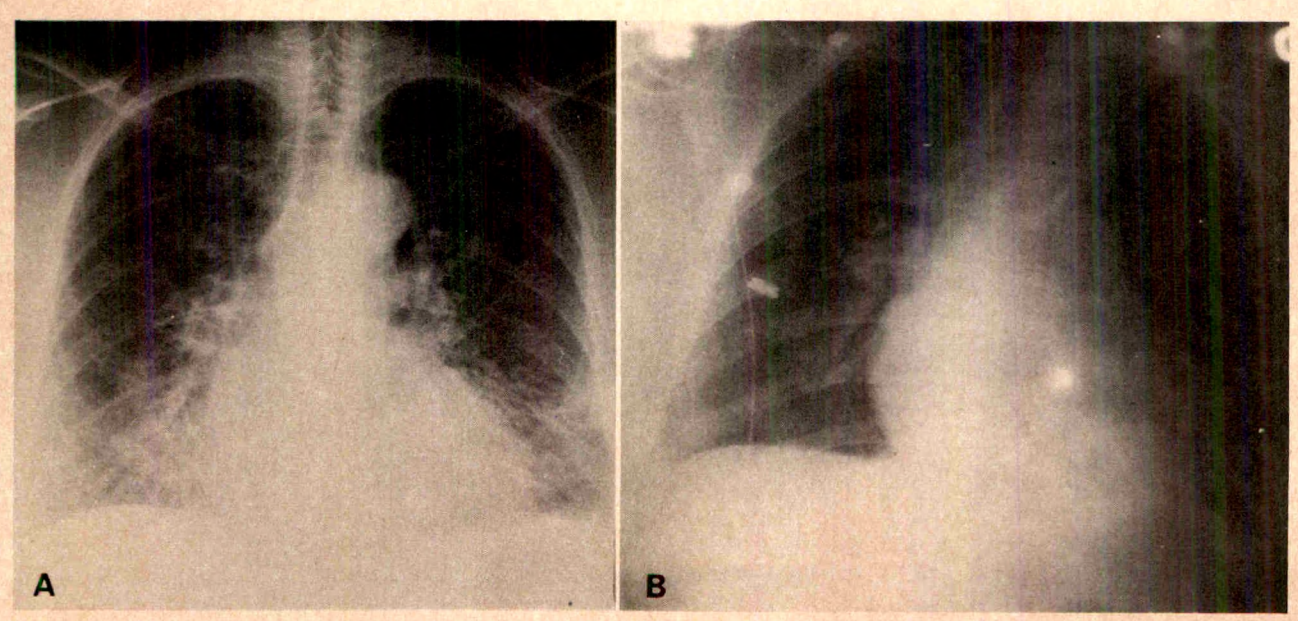

Figure 11. Case 4. Chest roentgenogram before dual-chambered intraaortic balloon pumping (**A**) and after 30 minutes of assistance (**B**), demonstrating rapid clearing of pulmonary edema.

blood glucose or in urea levels during this period of time.

Pituitary secretion of growth hormone is known to be regulated by the hypothalamus. It is therefore tempting to speculate that secretion of growth hormone might have been stimulated during the periods of relative brain ischemia and that subsequent relief of the ischemia by the increased carotid blood flow during balloon assistance reversed this process. This view is supported by current studies carried out in our laboratories in animals with cardiogenic shock; increases of 30 to 40 percent in carotid blood flow were observed during intraaortic balloon pumping.

Discussion

Although the exact pathophysiologic mechanism of cardiogenic shock is not completely understood, a simplistic concept may look upon it as a vicious circle in which the infarct leads to a reduction in cardiac output producing a decrease in both blood pressure and coronary perfusion; this in turn leads to a decrease in coronary blood flow and to significantly more embarrassment of left ventricular function and a further decrease in coronary blood flow. In fact, the vicious circle may realistically be viewed as a spiral with death at its apex. Intraaortic balloon pumping attempts to interrupt this chain of events and to unwind the spiral in 2 ways: by increasing coronary blood flow and by decreasing left ventricular work. Many studies have related deterioration of left ventricular function to the acute reduction of coronary perfusion pressure and coronary blood flow, and the importance of trying to achieve maximal coronary blood flow in a patient with cardiogenic shock has been well emphasized. As Kuhn et al.[17] have pointed out, patients without acute myocardial ischemia may tolerate a similar reduction of coronary perfusion pressure. However, in patients in whom the greater portion of the myocardium ceases to contract, the remaining myocardium can take on an increased work load only if its blood supply is preserved. For the same reasons, drugs that have been beneficial in other forms of shock may not necessarily benefit patients with shock due to acute myocardial infarction. As Gunnar et al.[18] have shown, the use of agents, such as isoproterenol, which increase systolic pressure and cardiac output by their positive inotropic action but which also decrease diastolic and mean pressure by peripheral vasodilatation, may result in a decrease in coronary flow while increasing myocardial oxygen requirements. Indeed, Gunnar et al. observed 3 patients whose condition rapidly deteriorated and who died within minutes after isoproterenol was substituted for levarterenol. Death was presumed to have been caused by total pump failure that occurred after the sudden reduction in coronary blood flow through the noninfarcted myocardium. In general, then, it would appear that deterioration of left ventricular performance in cardiogenic shock is largely related to diminished coronary blood flow and that survival of the patient with a coronary occlusion is ultimately determined by a balance between the myocardial oxygen available and the oxygen requirements.[11]

Clinical results: The greatest increments in coronary blood flow are obtained with our dual-chambered intraaortic balloon, which maximizes the beneficial effects of mechanical assistance. Intraaortic balloon pumping with the dual-chambered balloon consistently increased coronary blood flow by 60 to 100 percent above the value obtained with the single balloon. The condition of all of our patients became hemodynamically stable during the period of assistance, and no patient had any demonstrable ill effects. The speed with which the sensorium cleared was most striking and points toward a possible use of intraaortic balloon pumping in cerebral ischemia. The effect on central venous pressure was consistent in all patients. With the onset of assistance, there was a rapid reduction in left ventricular end-diastolic pressure followed by a decrease in central venous pressure and prompt clearing of pulmonary edema. With this clinical improvement, patients who did not tolerate even minimal amounts of fluids before assistance were noted to require large volumes of colloid-containing solutions. Depletion of plasma volume has been suggested as a factor for the persistence of hypotension in these patients,[19–21] which in some may have resulted from the protracted use of levarterenol, known to produce an egress of fluid from the intravascular compartment.

Besides increasing coronary blood flow, intraaortic balloon pumping effectively reduces left ventricular work. The relative degree to which either of these components contributes to the overall improvement is difficult to assess. However, we would guess that some of the more immediate effects, such as clearing of pulmonary edema, are predominantly related to the unloading of the ventricle.

Mortality: With the marked improvement in the clinical status of the patients, 4 of 5 were returned to the coronary care unit; yet the overall mortality, in the final analysis, was not proportionately improved. This may simply be a reflection of the fact that the patients referred for mechanical support had had cardiogenic shock for many hours and were referred too late to be salvaged by any form of treatment. This view is supported by the fact that all of the 12 other patients who were referred for balloon pumping but who, for one reason or another, did not undergo pumping, died within 2 hours.

On the other hand, although intraaortic balloon

pumping improves many of the indexes of cardiogenic shock, in the final analysis it does not affect the totally infarcted myocardium itself, and the patient will relapse into intractable shock when the procedure is terminated if there is too little viable myocardium remaining.

Present indications: In 3 of our patients there was subsequent extension of their infarcts. This strongly suggests that only a more definitive therapy, such as infarctectomy or coronary revascularization, may salvage the patients. Intraaortic balloon pumping would then be an effective method of treatment to prepare a patient for possible cardiac surgery. This has been the experience of other groups.[8] However, there is evidence to indicate that the myocardial tissue surrounding the actual infarct is often functionally compromised by a relative decrease in coronary blood flow; with supportive therapy it is enabled to recover instead of progressing to necrosis.[22] Thus, balloon pumping may increase the functional myocardial mass and reduce the actual size of the ultimate infarct. At least in dogs, mechanical assistance diminished the size of experimentally produced infarcts[23] and increased collateral coronary blood flow.[24] More evidence is urgently needed to support this concept; if confirmed, it would lend strong support to the use of balloon pumping early in the treatment of disease.

At present, our indications for intraaortic balloon pumping are: (1) cardiogenic shock unresponsive to medical therapy, (2) intractable left ventricular failure, (3) need for pre- and postoperative assistance for cardiac surgery, (4) intractable angina pectoris (as a therapeutic trial), and (5) conditions benefited by a temporary increase in cerebral blood flow. Our experience suggests that intraaortic balloon pumping is a relatively innocuous procedure that should no longer be reserved for the hopeless case, but rather should be considered for the many potential candidates for circulatory assistance before they reach a preterminal state.

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Precordial S–T Segment Elevation Mapping: An Atraumatic Method for Assessing Alterations in the Extent of Myocardial Ischemic Injury

The Effects of Pharmacologic and Hemodynamic Interventions

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A noninvasive technique for evaluating the extent of myocardial ischemic injury after experimental coronary artery occlusion was devised and applied to study alterations in the extent of injury produced by hemodynamic and pharmacologic interventions. The technique was then extended to the assessment of myocardial ischemic injury in patients with acute myocardial infarction. In 7 closed chest dogs, electrocardiograms were recorded from 15 sites on the chest wall before and after intermittent occlusions of the left anterior descending coronary artery. There was no S–T segment elevation before the occlusion; 15 minutes after occlusion the sum of S–T segment elevations (ΣS–T) averaged 15.0 ± 3.0 mm (SEM, 1 mm deflection = 0.1 mv), and an average of 4.2 ± 0.6 sites exhibited elevations exceeding 0.1 mv (NS–T). Occlusions occurring during administration of isoproterenol (0.25 μg/kg per min) increased ΣS–T to 51.0 ± 9.0 mm and NS–T to 10.6 ± 0.9, whereas occlusions occurring after administration of propranolol (1 mg/kg) decreased ΣS–T to 3.0 ± 1.5 mm and NS–T to 0.2 ± 0.2. In 8 dogs the extent of ischemic injury, manifested by S–T segment changes, was decreased by propranolol and norepinephrine and increased by hemorrhagic hypotension and isoproterenol, applied up to 6 hours after occlusion.

Reproducible S–T segment maps, using 35 surface electrodes, were obtained in 19 patients with acute myocardial infarction. In 15 patients studied serially, ΣS–T decreased from 54.25 ± 7.00 to 38.50 ± 6.30 mm and NS–T from 18.7 ± 2.5 to 12.3 ± 2.8, respectively, during a 24 hour period. However, in 3 patients in whom ventricular fibrillation, arterial hypotension and further ischemic pain occurred, ΣS–T and NS–T increased whereas in another patient propranolol decreased ΣS–T and NS–T. Thus, precordial mapping, both in dogs and patients, shows changes parallel to those measured by the epicardial technique and should provide a useful clinical tool for determining acute changes in the extent of ischemic injury.

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The direction of S–T segment alterations in leads of the scalar electrocardiogram and the orientation of the S–T vector recorded by vectorcardiography are valuable in assessing the location of acute myocardial infarction.[1–9] It also is well recognized that extension of the S–T segment elevation during the evolution of an infarct may reflect enlargement of the injured zone.[10] Recently, we have shown in the open chest dog that the area of ischemic in-

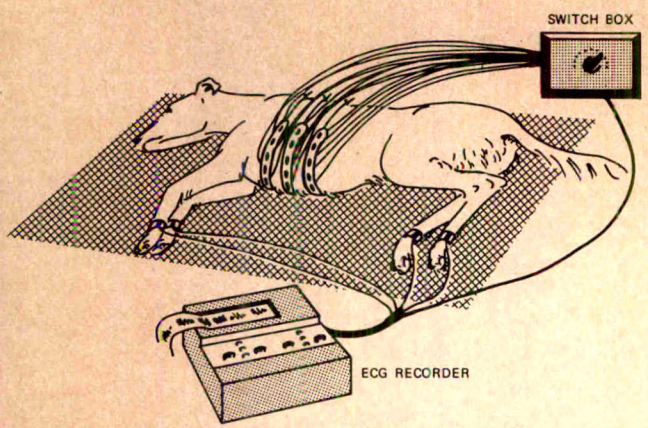

Figure 1. Placement of the 15 precordial electrodes in the dog.

jury can be identified from epicardial S–T segment elevation determined at numerous sites and that these electrocardiographic alterations correlate well with local myocardial creatine phosphokinase (CPK) depletion as well as with histologic signs of necrosis 24 hours later.[11,12] Hemodynamic and pharmacologic interventions that alter myocardial oxygen consumption or coronary perfusion were investigated by this technique and were found to alter substantially the size of the zone of myocardial damage. Despite its value in demonstrating alterations in the size of an ischemic zone in the experimental situation, this technique is, of course, not applicable in patients outside of the operating room. Accordingly, the present investigation was undertaken to develop a noninvasive method for evaluating the size of the zone of ischemic injury. This technique was applied to a study of the effects of several pharmacologic and hemodynamic influences on the size of this zone in the closed chest dog and then extended to an initial assessment of its applicability in patients with acute myocardial infarction.

Methods

Experimental studies: Studies were carried out in 15 dogs weighing between 18 and 22 kg and anesthetized with sodium thiamylal (25 mg/kg body weight). Respiration was maintained with a Harvard respirator. The heart was exposed through a left thoracotomy in the fifth intercostal space and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) or 1 of its branches was dissected from the adjacent tissues and either was fitted with a pneumatic cuff[13] to permit intermittent occlusions or was occluded permanently with a ligature. The pericardial cradle was then released and the chest closed and attached to underwater drainage by means of a self-retaining catheter. Limb lead electrocardiograms were taken in the standard fashion (Hewlett-Packard electrodes model 5721717, with Hewlett-Packard redux creme). Fifteen precordial leads (Hewlett-Packard model 14057) were placed in rows of 5 in the fourth, fifth and sixth left intercostal spaces between the midaxillary and the left parasternal lines and secured in a constant position by means of elastic straps (Fig. 1). These electrodes were attached to a switch box through the standard precordial unipolar lead. Arterial pressure was monitored with a Statham P23Db pressure transducer.

The extent and magnitude of ischemic injury was assessed by indexes similar to those previously described for epicardial electrocardiography[11]*:* the sum of S–T segment elevation in the 15 leads (ΣS–T) was used as an index of tissue injury (S–T elevation was expressed in mm, 1 mm = 0.1 mv), and the number of sites at which the S–T segment elevation exceeded 0.1 mv (NS–T) was taken to reflect the extent of myocardial ischemic injury. The data were analyzed by the paired *t* test technique when the effects of various interventions on these 2 variables were determined in the same animal.

In the first group of experiments, performed on 7 dogs, intermittent 20 minute occlusions were carried out by inflating the pneumatic cuff. Successive occlusions were separated by at least 1 hour to ensure a return to control conditions. The first occlusion was without any pharmacologic intervention. Five minutes before the second occlusion, an infusion of isoproterenol (0.25 μg/kg per min) was begun and continued throughout the 20 minute period of occlusion. The third occlusion followed 5 minutes after the intravenous injection of propranolol (1 mg/kg). The classic electrocardiographic limb leads and the 15 precordial leads were recorded before and 5, 10, 15 and 20 minutes after the onset of each occlusion.

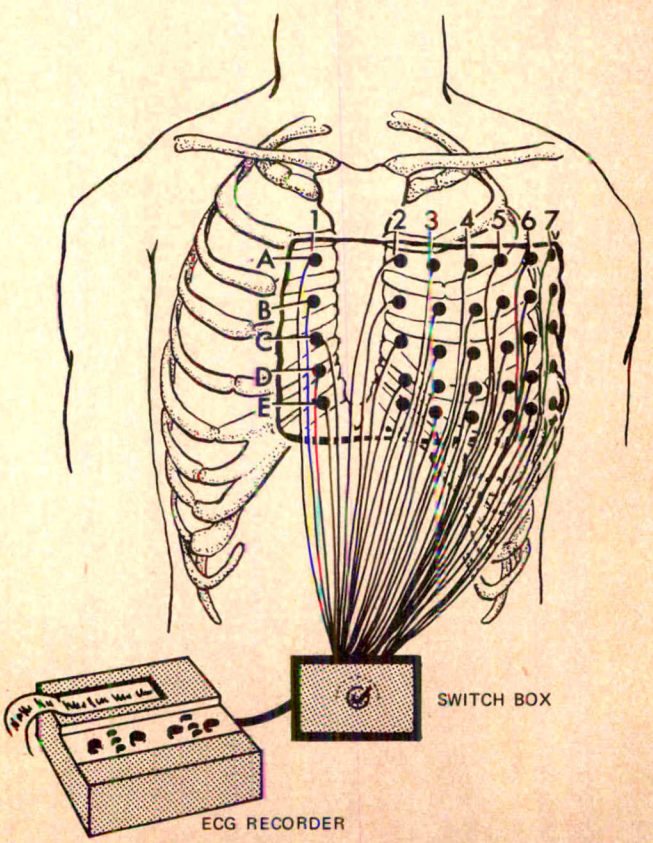

Figure 2. Schematic representation of the 35 electrode set on a patient's chest.

In the second group of experiments, performed on 8 dogs, the coronary artery was permanently ligated, and various interventions were subsequently carried out at intervals up to 6 hours. These included the infusion of isoproterenol (0.12 to 0.50 μg/kg per min, 5 dogs), norepinephrine (0.01 mg/kg per min, 3 dogs) and propranolol (1 mg per kg, 5 dogs), and the induction of hemorrhagic hypotension (4 dogs). The 15 chest leads were recorded at intervals of 5 minutes. Arterial pressure was monitored continuously.

Clinical studies: In 19 patients (11 male and 8 female), precordial electrocardiograms were recorded with a 35 electrode blanket (Fig. 2). The electrodes (Hewlett-Packard model 14057, filled with Hewlett-Packard redux creme) were arranged in 5 horizontal rows of 7 leads each. The 5 horizontal rows were designated by the letters A to E, with A the top and E the bottom row; the 7 vertical columns were designated 1 to 7, with 1 the extreme right and 7 the extreme left vertical column. The top right electrode (A1) was placed in the second intercostal space at the right parasternal line and in this way the bottom left lead (E7) was at or close to the sixth intercostal space at the midaxillary line. The distance between vertical columns 1 and 2 was 7 cm, and between all of the other adjacent vertical columns 4.5 cm. The distance between adjacent horizontal rows was 4 cm. The 35 electrodes were connected to a switch box that was in turn connected to the electrocardiograph through the "V" lead. The limb leads were connected in the usual fashion.

The precordial electrocardiograms in patients were analyzed using the same indexes described for dogs: the sum of S–T segment elevations (ΣS–T), and the number of sites in which S–T segment elevations exceeded 0.1 mv (NS–T). S–T segment elevations were always analyzed independently by 2 observers. Nineteen patients who entered the coronary care unit and in whom the diagnosis of acute myocardial infarction was confirmed were studied 1 to 8 times, and a total of 78 sets of electrocardiograms were recorded in them. The localization of the acute myocardial infarction in these 19 patients was as follows: anterolateral 11; anteroseptal 3; inferoposterior 2; anteroinferior 2; and inferior 1.

Results

Studies in Dogs

Simple coronary occlusion: The average ΣS–T from the 15 precordial sites was 0 before occlusion and increased to 15.0 ± 3.0 mm (SEM) 15 minutes after occlusion in 7 experiments. Similarly, the number of sites with S–T segment elevations exceeding 0.1 mv (NS–T) increased from 0 to 4.2 ± 0.9 (Fig. 3). The most commonly altered leads were in the fourth and fifth intercostal spaces on the ventral surface, whereas the more dorsal leads generally remained normal, and served as control leads.

Isoproterenol: Administration of isoproterenol (0.25 μg/kg per min) to 6 dogs increased the average heart rate from 142 ± 11 to 173 ± 11 beats/min, whereas mean arterial presure declined from 122 ± 8 to 109 ± 7 mm Hg. The average ΣS–T 15

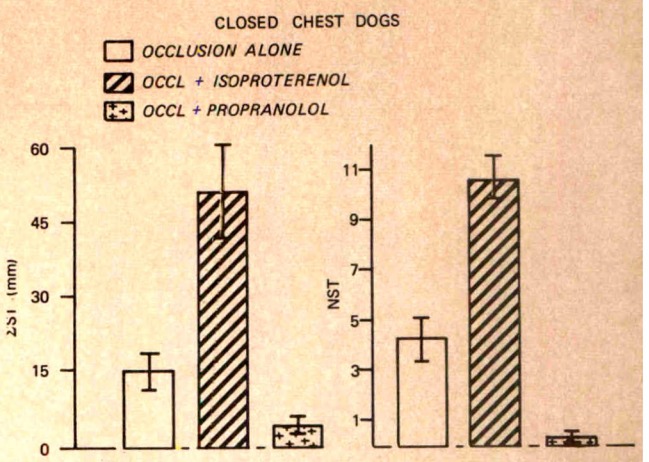

Figure 3. Summary of the results in group 1 (intermittent coronary occlusion) (7 dogs). Changes in average ΣS–T (**left panel**) and average NS–T (**right panel**) 15 minutes after occlusion alone (bars at **left**), after occlusion during infusion of isoproterenol (**middle bars**) and after occlusion after administration of propranolol (bars at **right**). Brackets indicate ±1 SEM.

minutes after occlusion increased from 15.0 ± 3.0 mm after simple occlusion to 51.0 ± 9.0 mm ($P < 0.01$) after an occlusion in the presence of isoproterenol, and NS–T rose from 4.2 ± 0.9 to 10.6 ± 0.9 ($P < 0.01$) (Fig. 3 to 5). Isoproterenol (0.12 to 0.5 μg/kg per min) was also administered on 7 occasions to 5 dogs in the second group at intervals up to 6 hours after a continuously maintained coronary occlusion. Within 10 minutes of the onset of isoproterenol infusion average ΣS–T increased from 7.5 ± 6.0 to 30.0 ± 12.0 mm ($P < 0.05$) and NS–T from 2.2 ± 1.7 to 7.8 ± 1.7 ($P < 0.05$). In 3 animals in which there was no S–T segment elevation in any precordial lead after oc-

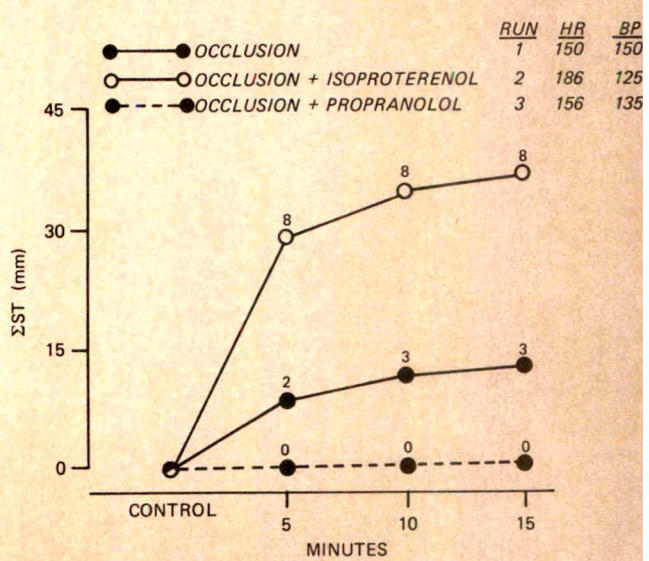

Figure 4. An example from an experiment in group 1 showing the effects on ΣS–T of a simple occlusion, occlusion during infusion of isoproterenol and occlusion after administration of propranolol. Minutes = minutes after coronary occlusion. NS–T is indicated by the numbers over the ΣS–T points at each time.

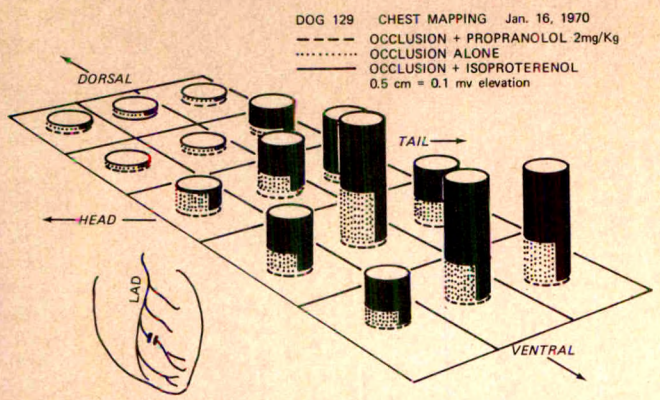

Figure 5. Schematic representation of S–T segment elevation in each of the 15 precordial sites after occlusion alone, occlusion during the infusion of isoproterenol and occlusion after administration of propranolol. Insert is schematic representation of the heart showing occlusion of the apical branch. (The experiment depicted is the same as in Fig. 4.)

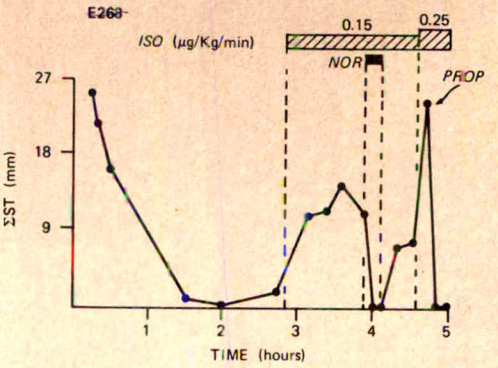

Figure 6. Experiment from group 2 (animals with permanent coronary occlusion). The S–T segment elevation decreased spontaneously but reappeared with infusion of isoproterenol (ISO). This S–T segment elevation could be reversed by infusion of norepinephrine (NOR) (0.01 mg/kg per min), which increased mean arterial pressure from 104 to 125 mm Hg (4 hours after occlusion) or by administration of propranolol (PROP) (1 mg/kg) 4½ hours after occlusion.

clusion, the administration of isoproterenol induced S–T segment elevation (Fig. 6). In these 3 dogs this evidence of injury could be completely reversed by administration of 1 mg/kg of propranolol (ΣS–T decreased from an average of 24.0 to 0 mm, and NS–T from 8.3 to 0).

Propranolol: The administration of propranolol (1 mg/kg) to 6 dogs in group 1 decreased the average heart rate from 150 ± 7 to 137 ± 10 beats/min, whereas mean arterial pressure remained unchanged at an average level of 125 ± 6 mm Hg; ΣS–T decreased from 15.0 ± 3.0 after simple occlusion to 3.0 ± 1.5 mm after occlusion with propranolol ($P < 0.01$) and NS–T decreased from 4.2 ± 0.9 to 0.2 ± 0.2 ($P < 0.01$, Fig. 3 to 5).

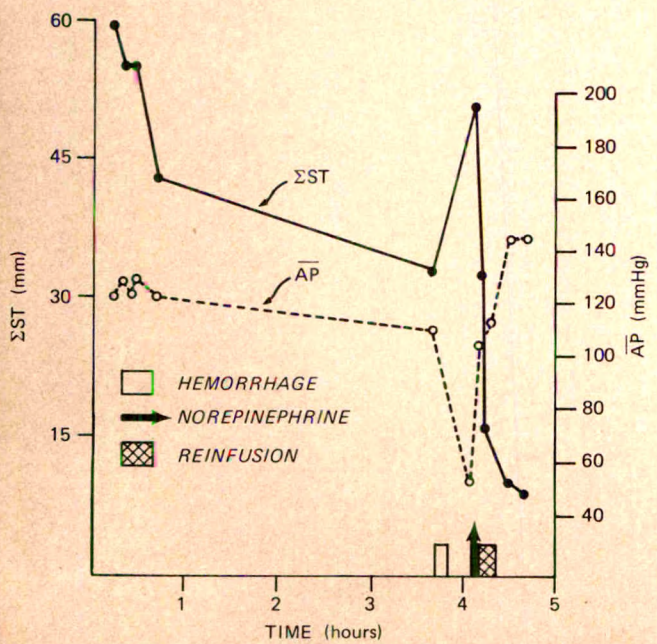

Figure 7. Experiment from group 2. The effects of hemorrhage, norepinephrine and reinfusion on ΣS–T are shown successively. $\overline{AP}$ = mean systemic arterial pressure.

In 5 animals in group 2 propranolol was given from 1 to 5½ hours after a continuously maintained occlusion, and in all cases within 10 minutes of its administration there was a striking fall in ΣS–T and NS–T; the average ΣS–T fell from 42.0 ± 13.5 to 24.0 ± 13.5 mm ($P < 0.05$) and the average NS–T from 10.2 ± 1.2 to 5.4 ± 2.1 ($P < 0.05$). These decreases were also observed when the area of injury was maintained by continuous isoproterenol infusion (Fig. 6).

Norepinephrine: In 4 dogs (3 in group 2 and 1 in group 1), administration of norepinephrine (0.01 mg/kg per min) was begun at various times up to 4 hours after occlusion; mean arterial pressure increased from an average of 68 to 122 mm Hg, and heart rate decreased from 155 to 145 beats/min. The average value for ΣS–T fell from 33.0 ± 13.5 to 7.5 ± 3.0 mm ($P < 0.05$) and for NS–T from 7.0 ± 2.3 to 3.7 ± 0.8 ($P < 0.01$) (Fig. 6 and 7).

Hemorrhagic hypotension: In 5 dogs (4 in group 2 and 1 in group 1), hemorrhagic hypotension was produced by arterial bleeding; mean arterial pressure decreased from 114 to 64 mm Hg, whereas average heart rate remained unaltered (Fig. 7). In all instances ΣS–T increased, from an average of 18.0 ± 6.0 to 55.5 ± 6.0 mm ($P < 0.01$), and NS–T increased from 6.0 ± 2.1 to 11.0 ± 0.8 ($P < 0.05$). Reinfusion in 2 experiments raised mean arterial pressure from 40 and 50 to 95 and 135 mm Hg, respectively, and decreased ΣS–T from 66.0 and 52.5 to 28.5 and 10.5 mm, respectively, whereas NS–T fell from 11 and 13 to 8 and 1, respectively.

Clinical Studies

Measurements of ΣS–T in the precordial tracings varied within 3 percent between the 2 observers, and their recorded values of NS–T were identical. In 6 patients who were in a stable state the

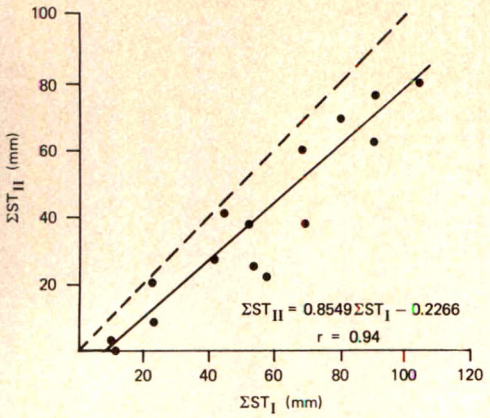

Figure 8. Fall in the sum of S–T segment elevation in 24 hours. ΣST_I = the sum of S–T segment elevation on the first day; ΣST_{II} = the sum of S–T segment elevation 24 hours later. The **solid line** is the regression line, and the **dashed line** is the identity function.

multielectrode blanket was positioned on the patient's chest and a precordial electrocardiographic map was recorded; the blanket was removed and 15 minutes later replaced on the patient's chest and the map rerecorded; the maximal difference in ΣS–T and NS–T between duplicate measurements was 5 percent.

Serial studies were carried out only in the 15 patients with acute infarcts involving the anteroseptal and the anterior and lateral walls of the left ventricle, that is, patients in whom the area of S–T segment elevation could be covered by the electrodes within the blanket. The first observation was made within 24 hours after the patient's admission and the second on the following day; during this interval ΣS–T decreased from 54.25 ± 7.00 to 38.50 ± 6.30 mm ($P < 0.01$), a decline of 29 percent, and NS–T decreased from 18.7 ± 2.5 to 12.3 ± 2.8 ($P < 0.01$) in 24 hours. The relation between ΣS–T on the first day ($\Sigma S–T_I$) and on the second day ($\Sigma S–T_{II}$) could be expressed as follows: $\Sigma S–T_{II} = 0.8549\ \Sigma S–T_I - 7.93$, $r = 0.94$ (Fig. 8).

In 3 other patients there was an increase in the intensity and extent of ischemic injury. In the first patient, after a recurrent bout of pain of myocardial ischemia, ΣS–T increased from 59.5 to 80.5 mm and NS–T from 20 to 33 (Fig. 9, A and B). In the second, a patient with chronic systemic arterial hypertension, a reduction in arterial pressure from 170/130 to 130/90 mm Hg induced by intravenous hydralazine increased ΣS–T from 49 to 70 mm and NS–T from 22 to 27. In a third patient, after an episode of ventricular fibrillation, ΣS–T increased from 17 to 42 mm and NS–T from 5 to 14. On the other hand, 1 patient was given propranolol (5 mg intravenously) as an antiarrhythmic agent; ΣS–T decreased from 91.0 to 42.0 mm and NS–T from 29 to 17 within 1 hour, whereas the heart rate decreased from 145 to 100 beats/min (Fig. 10).

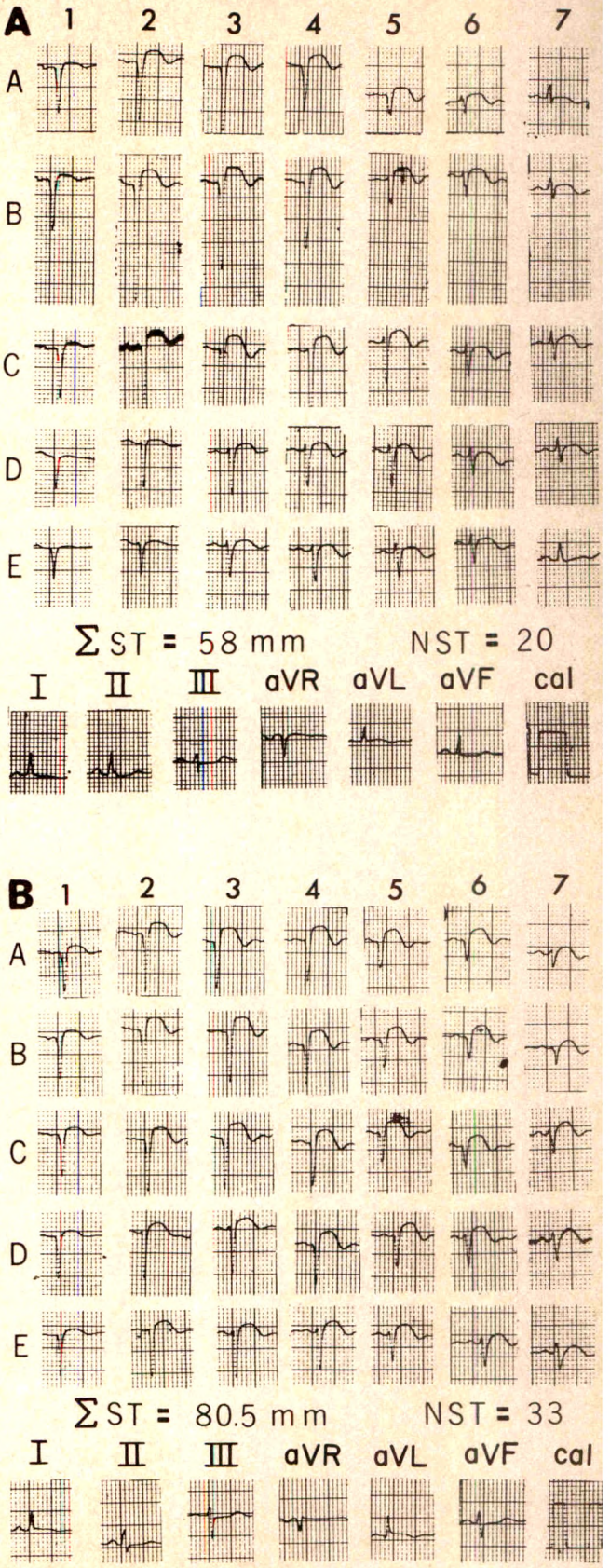

Figure 9. **A,** 35 precordial electrocardiograms and frontal plane leads in a patient with an acute myocardial infarction. **B,** the electrocardiographic map in the same patient on the following day, after the development of another episode of pain of myocardial ischemia.

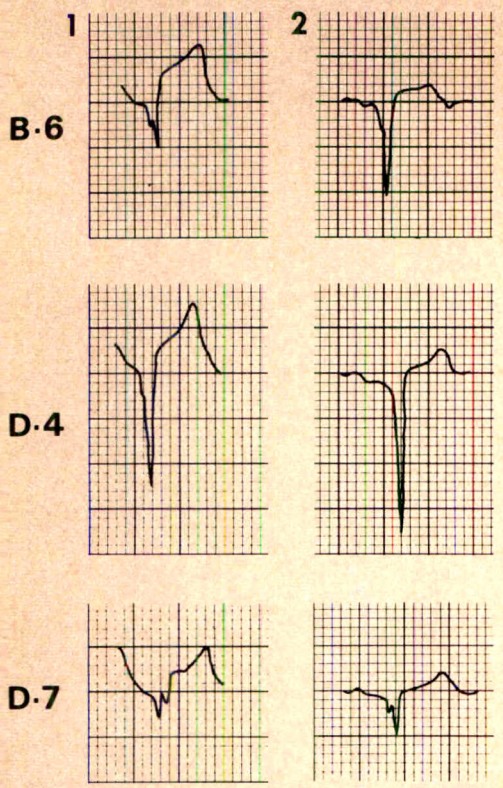

Figure 10. The influence of propranolol on S–T segment elevation in a 50 year old man with acute myocardial infarction. Column 1, immediately before administration of propranolol; column 2, 1 hour after administration (5 mg intravenously).

Discussion

With the ability to detect and treat successfully most primary arrhythmias in the coronary care unit, increasing attention is being directed to the detection and treatment of pump failure, now by far the most common cause of in-hospital death in patients with acute myocardial infarction. In recent years considerable effort has been directed to monitoring hemodynamic changes in patients with acute myocardial infarction, and hemodynamic findings have been used to establish prognosis and thereby to modify treatment.[14,15] Pump failure results primarily from ischemic loss of normally contractile myocardium, and at postmortem examination, patients who succumb to cardiogenic shock uniformly show massive areas of infarction.[16] Therefore, it is of critical importance to find ways to assess changes in the extent of ischemic injury and to reduce it. The latter may be accomplished (1) by lowering myocardial needs for oxygen in areas of heart muscle in which perfusion has been markedly reduced by coronary occlusion but is not totally absent, or (2) by increasing the delivery of oxygen to such areas.

Recently we have shown by means of epicardial electrocardiography that profound alterations in the area of ischemic injury can be produced by hemodynamic and pharmacologic interventions that alter myocardial oxygen consumption or coronary perfusion pressure.[11] The area of ischemic injury detected by epicardial leads may be used to predict the extent of necrosis quantitatively reflected by myocardial creatine phosphokinase depletion[11] and by histologic changes[12] 24 hours after occlusion. Obviously, this epicardial technique can be applied clinically only in the setting of the operating room,[17] and the present investigation was undertaken to develop a method of assessing myocardial injury which is clinically applicable.

Although the localization of an acute myocardial infarction is accomplished by the analysis of the distribution of S–T segment elevations in the 12 lead electrocardiogram,[1–9] the recognition and localization of some infarcts involving the basal portions of the lateral wall of the left ventricle,[18] or of the posterior wall,[19] require special leads. These leads should be recorded from intercostal spaces more cephalad than usual, in the case of high lateral infarcts,[18] and from multiple locations on the back and the right hemithorax for posterior infarcts.[19] This procedure is based on Wilson's concept[20] that the chest leads constitute "semi-direct" measurements of the electrical events of the immediately underlying myocardium. According to this theory, localized S–T segment changes on the epicardium are reflected in corresponding changes on the thoracic surface. The technique of precordial mapping utilized in the present investigation extends this principle, previously used for diagnosis and localization of cardiac damage, to an estimation of changes in the size of the zone of ischemic injury. This method appears to make it possible to determine the effects of alterations of the hemodynamic state or of pharmacologic agents on the extent and severity of such injury, and it opens the possibility of immediately assessing the beneficial or deleterious effects of different modes of treatment on the ischemic zone at the patient's bedside.

Previous studies with multiple bipolar chest electrode techniques have been used to examine the electrophysiologic phenomena of impulse transmission and voltage distribution.[21–22] The present unipolar technique does not offer such means of analysis; rather, its only aim is to screen and monitor the extent of ischemic injury in the clinical setting; however, it is similarly based on the multipolar concept.

Effect of pharmacologic and hemodynamic interventions on extent and severity of ischemic injury: Using the thoracic mapping method in closed chest dogs, isoproterenol increased ΣS–T by 340 percent and NS–T by 250 percent, values comparable to those observed when epicardial methods were employed to assess the effects of this drug.[11] It was also observed that, whereas isoproterenol infusion and arterial hypotension increased the extent and severity of ischemic injury, propranolol exerted the opposite effect. The action of isoproterenol re-

sulted presumably from an increase in oxygen requirements of inadequately perfused areas of myocardium, whereas it seems likely that the effect of propranolol resulted from a reduction in myocardial oxygen needs. Hypotension exerted an effect similar to isoproterenol, probably by further reducing the perfusion of this critical zone and thereby augmenting the unfavorable balance between myocardial oxygen supply and demand. Norepinephrine decreased the area of injury, presumably because the augmented myocardial perfusion resulting from increased coronary perfusion pressure increased oxygen delivery more than this drug stimulated myocardial oxygen consumption.

These interventions in experimental animals were applied before as well as up to 6 hours after coronary occlusion. They exerted similar effects in all of these studies, thereby demonstrating the feasibility of altering the extent and severity of ischemic injury a number of hours after a coronary occlusion. These studies have particular clinical relevance, since they deal with the period when most patients with acute myocardial infarction have already reached the coronary care unit.

The instances of coronary occlusion in animals without S–T segment elevation were of particular interest. These dogs presumably possessed sufficient collateral circulation to provide adequate oxygenation of the myocardium distal to the obstructed vessel. However, even in these animals, the administration of isoproterenol induced the appearance of a zone of injury, thereby suggesting that the increases in oxygen demands provoked by the positive inotropic and chronotropic effects of isoproterenol produced ischemia in myocardium perfused only by collateral vessels. This deleterious action of isoproterenol could be reversed by beta adrenergic blockade with propranolol.

Clinical implications: The data obtained from patients with acute myocardial infarction with the 35 lead precordial map permitted study of the natural course of changes in S–T segment elevation, and in several instances observation of the effects of hemodynamic changes or of drug administration on the severity and extent of myocardial injury. It was observed that in the clinical setting the technique is adequately reproducible and shows little interobserver variation. In patients with uncomplicated myocardial infarcts the decrease in ΣS–T during the course of 24 hours was found to average 29 percent. However, in individual patients ΣS–T and NS–T were found to increase as a consequence of arterial hypotension, after recurrence of ischemic chest pain, and after ventricular fibrillation and in 1 instance to decrease strikingly after propranolol administration. Although the number of patients with acute myocardial infarction in whom hemodynamic changes occurred or in whom the effects of drug administration were studied is very limited, all of the observations are in accord with those made initially in open chest dogs[11] and with those reported here in the closed chest dogs. A systematic examination of the effects of several of these influences on S–T segment precordial maps of patients with acute myocardial infarction currently is under way. The present study included only patients with anteroseptal, extensive anterior, lateral and high lateral infarcts. In addition, patients with "true" posterior wall infarcts were also diagnosed and screened by putting the blanket on their back. However, this method is not useful in patients with inferior wall infarcts.

In conclusion, the recording of S–T segments from multiple thoracic leads provides a noninvasive technique for monitoring changes in the area of ischemic injury in closed chest dogs undergoing experimental coronary occlusion as well as in patients with acute myocardial infarction. This measurement enabled us to extend the information previously obtained in open chest dogs and to observe in closed chest dogs that the extent and magnitude of ischemic injury change in accordance with the balance between oxygen supply and demand for at least 6 hours after coronary occlusion. Finally, observations in patients indicate that a predictable reduction in the magnitude of S–T segment elevation occurs with time and suggest that influences that affect the magnitude of ischemic injury in the experimental animal are also operative in patients with acute myocardial infarction.

Acknowledgment

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The Role of Viruses in the Production of Heart Disease

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Clinical and experimental evidence for the role of viruses in the production of heart disease in man is reviewed. The data indicate that viral myocarditis, viral endocarditis, viral pericarditis and viral pancarditis are true entities that must be considered by clinicians in diagnosis and treatment of patients. It is suggested that viruses may be involved in the production of chronic heart disease and that "conditioning" factors possibly including streptococcal infections are important, both in the original infection and in activation of latent or dormant viruses. Viral infections may be responsible for much heart muscle disease, that is, cardiomyopathy, as well as for "rheumatic heart disease" of undetermined origin. The role of viruses, particularly rubella and Coxsackie, in the production of congenital heart disease is emphasized. Conceivably, viral infection acquired in utero might produce heart disease later in life. Many viruses are known to cause clinical pericarditis, some followed by chronic constriction. A possible role of viruses in the production of the postpericardiotomy syndrome or cardiac causalgia is suggested.

Measures for the prevention of viral heart disease and methods of treatment, with particular emphasis on prolonged bed rest, are discussed. The need for laboratory facilities for routine viral studies is stressed.

It is well established that viruses cause heart disease in man.[1,2] However, precisely how and the extent to which viruses cause cardiovascular disease in man need investigation. The purpose of this brief review is to examine some of the present clinical and experimental evidence of the role of viruses in the production of heart disease in man and to indicate the significance of viral heart disease in medicine.

Concepts and Mechanisms of Viral Heart Disease

Broad concepts of the nature of viral infections are necessary to appreciate fully the possible role of viruses in the production of heart disease[3,4] (Fig. 1). For example, it must be realized that most viral infections are not clinically recognizable, that is, they are subclinical infections and include infections by slow or dormant viruses. Moreover, when a clinically apparent infection does occur, it may present a variety of pathologic and symptomatic manifestations; for example, the same enterovirus may produce all or only 1 of the following: rash, meningitis, gastroenteritis, "common cold," or myocarditis.

Mechanisms by which viruses might produce myocardial disease include direct invasion of the myocytes by the virus, involvement of the central nervous system with secondary myocardial

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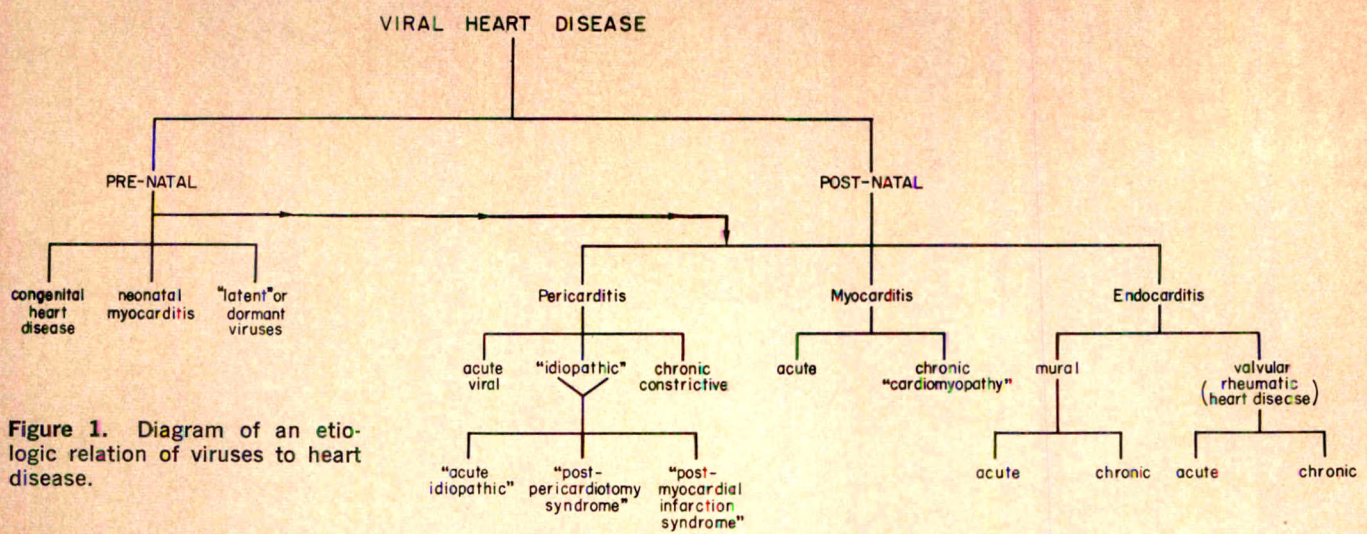

Figure 1. Diagram of an etiologic relation of viruses to heart disease.

damage, disturbances in cellular metabolism, disturbances of vascular supply to the myocytes, and possible elaboration of toxins and antigen-antibody reactions, that is, "allergic" or "autoimmune" phenomena.[5]

Hypersensitivity reactions: "Allergic" or "autoimmune" reactions to viruses or following viral infections and tissue destruction are of theoretical interest in the production of many diseases including viral heart disease.[3,6,7] Evidence for such reactions is inadequate to establish fully such concepts. However, it has been postulated that infection and initial proliferation of the virus are followed by a latent period after which lesions are produced which resemble hypersensitivity reactions.[8] The infecting organism cannot be recovered from these postinfectious lesions which differ histologically from lesions that occur during the initial infection. These hypersensitivity reactions are generally of the "delayed" type, that is, dependent on cellular immune mechanisms. The possibility exists that such immune processes might continue after the viral infection of the heart and in turn produce chronic myocardial injury, for example, chronic cardiomyopathy.[9] The finding of virus-like particles in germ-free NZB mice indicates that such mice may provide an animal model for the study of the possible role of viruses in autoimmune disease.[7]

Conditioning factors: The possibility for latent or slow viruses to produce disease is considerable. Such viruses lie dormant in certain areas of the body only to become apparent when appropriately stimulated or when conditioning factors present themselves. For example, the virus of herpes simplex may produce disease ("fever blisters") when stimulated by fever, emotional stress, malaria, pneumococcic pneumonia or solar trauma.

The roles of mixed viral and bacterial infections in the production of disease have recently been reviewed by Loosli[10] and others.[11,12] In certain situations virus and bacteria may act synergistically or through still obscure conditioning mechanisms to produce more extensive disease together than either agent would produce alone. In some instances one disease-producing agent, such as a bacterium, may have to be present in order for infection to occur with the other, e.g. a virus.[10] In fact, bacteria may contain virus pathogenic for man.

The importance of "conditioning factors" in the initiation of viral disease must also be appreciated. Experimental evidence for the role of conditioning factors in the production of viral myocardial disease has been presented by Pearce,[13] who found that myocarditis produced in rabbits by virus III could be greatly increased in incidence and severity by physically traumatizing the myocardium with a needle puncture. Other conditioning factors include alcohol, pregnancy, malnutrition, steroids, ionizing radiation and heat. None of these or other such factors have received sufficient attention with respect to man. The effects of exposure to cold and humid weather, or drafts, or becoming chilled on the production of respiratory tract infections with both bacterial and viral agents are well known and accepted by laymen, if not by all microbiologists.

Viral infections acquired in utero: Viral infections occurring in utero produce a significant amount of heart disease. For example, the rubella virus is known to produce congenital cardiac disease, as well as other anomalies, when infection occurs during the early embryonic stage of development.[14] The same has been found to be true for Coxsackie viruses,[15–17] whereas other viruses seem to be less cardiotropic in this respect.

When infection occurs after the heart is formed, only neonatal inflammatory myocardial disease occurs. Even more intriguing is the possibility that viruses acquired in utero might lie dormant in the myocardium only to become activated later in life by proper and potent conditioning factors to produce clinical cardiac disease of many types.[16] Transmission of viruses by gametes and genetically determined conditioning factors and the type of diseases that might be produced are uncharted

fields of study. There must be many unknown cardiotropic viruses peculiar to certain areas of the world and infectious for specific animal species. The incidence of stillbirths secondary to viral heart disease in the fetus remains to be determined. The Coxsackie virus in pregnant mice not only produces acute myocarditis in the fetus which resembles Fiedler's myocarditis but also produces stillbirths (unpublished data).

Clinical classification: The clinical classification of viral diseases of the heart into those involving the pericardium, myocardium, endocardium or all layers of the heart simultaneously is purely arbitrary since is it likely that in any given patient with viral heart disease, some virus may be found in the cells of all cardiac layers simultaneously. For example, in clinical viral pericarditis, the electrocardiographic changes are due to involvement of the myocardium by the disease process and not to the pericarditis itself. Thus, myopericarditis has been suggested as an encompassing term for Coxsackie infections that involve the myocardium or pericardium or both. Separation of viral diseases of the heart into acute and chronic is also arbitrary. There is a tremendous overlap between these disease categories. For example, any acute infection probably causes permanent changes in the myocardium even though these may be subtle and result in no clinically detectable cardiac disease. However, acute viral infections of the heart may persist and produce chronic heart disease (Fig. 1). In some instances the initial tissue destruction and subsequent healing process alone are enough to result in chronic myocardial dysfunction.

Because the usual classification of viral heart disease is clinically convenient, the viral diseases to be discussed are considered accordingly. The signs and symptoms of the various types of viral heart disease are not discussed in detail except those which, in our opinion, are not generally appreciated.

Clinical Considerations

The diagnosis of viral heart disease in man is usually entirely indirect, that is, obtained by clinical logic. The clinical findings, isolation of the virus from the stool, pharyngeal washings and other body fluids, and change in specific viral antibody titre all contribute to establishing a clinical diagnosis. Regardless of whether the final clinical diagnosis is that of pericarditis, myocarditis, endocarditis or pancarditis, the patient often gives the history of a preceding, nonspecific febrile illness, usually upper respiratory. In certain viral infections the initial clinical findings may be sufficiently typical to make a diagnosis of viral nasopharyngitis, tonsillitis, paranasal sinusitis, mumps, or the like. Unfortunately, unless the disease is a well known viral disease, such as mumps or measles, the clinician too often assumes an upper respiratory tract infection to be bacterial. Because clinicians can isolate bacterial agents with ease, they may fail to realize that an attempt to isolate viruses has not been made. Moreover, bacteria can be isolated from a normal throat, sinuses or nares. Thus, the mere isolation of bacteria does not necessarily indicate the absence of pathogenic viruses or eliminate the possibility that both viruses and bacteria are acting in a necessary correlated fashion to produce the patient's illness.

In some patients cardiac involvement may be evident at the start of a viral illness, but there is usually a latent period of several days during which the patient is asymptomatic. This interval is then followed by clinical evidence of cardiac disease as manifested by the well known symptoms and signs of pericarditis, myocarditis or endocarditis, alone or in combination. Thus, because of such temporally related phenomena, the physician and others have difficulty relating an infection regardless of type, to the cardiac disease. Viral diseases often produce a leukocytosis instead of the usually expected lymphocytic response.

The electrocardiogram of patients with viral heart disease may show classic changes of acute pericarditis, or the changes may be nonspecific with T wave inversion, S–T segment abnormalities, various types of atrioventricular conduction disturbances or, occasionally, patterns that resemble electrocardiographic changes of myocardial infarction due to electrical silence produced by fairly large isolated areas of myocardial damage.

Pericarditis

Table I lists the various probable and possible viral causes of acute pericarditis.

Idiopathic Pericarditis

Christian in 1951 wrote the following about idiopathic pericarditis: "However, the word, idiopathic, probably is not justified. It simply means that the exact cause is not known." He then added "Very possibly, under the conditions cited, the cause is a virus."[18] Since 1951 many specific viruses have been isolated that produce acute "idiopathic" pericarditis.[19] Because the clinical picture of "idiopathic" pericarditis is often preceded by a respiratory-like infection,[20,21] studies have been conducted in search for specific respiratory viruses in sporadic cases,[21,22] often with a low yield.[21] However, such results should be expected not only because viruses are difficult to isolate but because one usually finds only that for which one searches. For example, when a special effort was made to isolate Coxsackie viruses in patients with idiopathic pericarditis,[23] a large number of these viruses were found. Therefore, it is likely that viruses cause most, if not all, acute "idiopathic" pericarditis. Unfortunately, it often requires an exhausting search to find the specific etiologic agent from among the 400 or more currently known viruses. Nevertheless, such a search should

TABLE I

Some Viruses That Cause Heart Disease in Man

Disease	Virus
Pericarditis	Coxsackie (B and A)
	ECHO
	Mumps
	Chickenpox (herpes zoster)
	Herpes simplex
	Poliomyelitis
	Influenza
	Adenovirus
	Infectious mononucleosis
Myocarditis	Coxsackie (B and A)
	Poliomyelitis
	Influenza
	Adenovirus
	ECHO
	Cytomegalovirus
	Rubeola
	Rubella
	Chickenpox (herpes zoster)
	Rabies
	Hepatitis, infectious
	Smallpox
	Yellow fever
	Lymphocytic choriomeningitis
	Epidemic hemorrhagic fever
Endocarditis	Coxsackie (B and A)

not only be possible but required for elegant cardiologic practice.

Viral Causes of Pericarditis

Coxsackie viruses: Of all viruses, the Coxsackie B group has been most firmly linked with clinically evident pericarditis[9,24]; however, Coxsackie A viruses have also been found to produce pericarditis. By 1964, more than 50 cases had been reported with laboratory evidence for a Coxsackie B viral origin.[25] The most convincing evidence for the Coxsackie viral origin of pericarditis is found when isolation of the virus from the feces or pericardial fluid, or both,[26] is accompanied by diagnostic increases in neutralizing antibody titer, common findings during epidemics of Coxsackie infection.[27,28] With use of the immunofluorescent technique, Coxsackie B_4 antigen was found at necropsy within the pericardium of a patient who had clinical and histologic evidence of pericarditis, providing additional direct evidence that the Coxsackie viruses can infect the pericardium.[29] Experimentally, Coxsackie virus B_4 infection produces epimyocarditis with pericarditis in cynomolgus monkeys[30] (Fig. 2) and in mice.[31]

EB virus: Infectious mononucleosis has long been considered a viral illness. However, only recently has evidence for the existence of the etiologic viral agent been found. The EB (Epstein-Barr) virus, a herpes-like virus, is now accepted as the probable etiologic agent.[32] Acute pericarditis was first associated with infectious mononucleosis by Evans and Graybird in 1946.[33] Since that time many such associations have been recorded.[34]

Influenza and other viruses: Pericarditis has been described in patients infected with influenza B virus.[22] Influenza A, Asian type, virus was recovered from the pericardial fluid of a patient with pericarditis and a history of "rheumatic" heart disease who, at necropsy, had an increase in interstitial connective tissue and Aschoff bodies.[35] In another patient with pericarditis, influenza virus A_2 was isolated from the pericardial fluid.[36] Evidence for ECHO viral origin of acute pericarditis was found when the virus was isolated from fecal material in association with a rise in specific neutralizing antibody titer.[21] Acute pericarditis secondary to mumps has been reported, but not with recovery of the virus.[21,37] A patient with pericarditis and chickenpox has been described.[38] Many other viruses[1,2] (Table I), and probably some as yet undiscovered, produce pericarditis. It is obvious that, until proper laboratory facilities are generally available for the diagnosis of viral diseases, isolation of the specific viral etiologic agent in a patient with pericarditis will be a formidable task.

Pericarditis of Possible Viral Cause

An interesting febrile illness, which is associated with pericarditis and follows cardiac surgery, is the so-called postpericardiotomy syndrome.[39] The possibility that this syndrome might be the result of a de novo viral infection has been suggested.[40,41] However, another possible explanation is the activation of dormant, latent or slow virus by the trauma of cardiac surgery.[42] Myocardial infarction is also followed frequently by a syndrome resembling acute or mild idiopathic pericarditis. We have termed these syndromes *cardiac causalgia major* or *minor*.[43] One might speculate that viruses play a role in the production of these syndromes since the infarcted area might be conducive to viral infection[40] or because latent, dormant or slow viruses might become activated. Diseases of unknown origin in which pericarditis may be a prominent part of the clinical findings, for example, systemic lupus erythematosus, may also prove to be viral in origin.

Chronic Pericarditis

In most patients the prognosis after viral pericarditis is excellent[44]; nevertheless, chronic constrictive pericarditis has been shown to follow proved viral[28] as well as "idiopathic" pericarditis.[45,46] Therefore, in patients with constrictive pericarditis of "unknown" origin, consideration should be given to a possible viral cause.

Viral Myocarditis

Saphir[47] recognized that, although myocarditis was found in many patients at autopsy, the diag-

nosis of myocarditis was not often made before death. The clinical interest in viruses as a cause of myocarditis has increased over the past 10 to 15 years. A large number of viruses are now known to be capable of producing myocarditis.[1,2,48] However, only a few viruses are known to be highly cardiotropic for man. These cardiotropic viruses may serve as a prototype for other viral infections of the myocardium and should stimulate interest in viral etiology, not only of myocardial disease and various clinical expressions of cardiomyopathy, but also of many other lesions of the heart.

Coxsackie Viral Myocarditis

Since 1947, when the Coxsackie viruses were discovered by Dalldorf and Sickles,[49] there has been much interest in the Coxsackie viruses as causes of heart disease.[5,30,50,51] In 1952, the Coxsackie virus was first isolated from myocardial tissue of infants who died of acute myocarditis.[52] Many other reports of myocarditis in infants due to Coxsackie viral infections have since appeared. However, it was not until 1957 that Coxsackie viruses were shown to produce myocarditis in adults.[53] The clinical findings have been briefly described herein and in detail elsewhere.[5]

Both Coxsackie A and B viruses cause myocarditis. However, there are only 6 known serotypes of Coxsackie B viruses compared to 24 of Coxsackie A, which may explain why heart disease secondary to Coxsackie B is reported more frequently than that secondary to Coxsackie A viruses. Also, Coxsackie A virus is difficult to isolate in routine tissue culture.

Incidence: Although the exact incidence of myocardial disease produced by Coxsackie viruses is unknown, up to 39 percent of cases of unexplained myocarditis and pericarditis have been attributed to Coxsackie B viral infections.[50] It has been pointed out that some of the remaining cases are likely due to Coxsackie A viral infections. This highly cardiotropic and prevalent group of viruses thus provides an etiology for a large amount of unexplained heart disease in man.[50] Outbreaks of Coxsackie viral infection have already revealed that a large number (33 percent) of patients will develop some form of myocardial disease[54] as a result of the infection.

Because evidence of Coxsackie B viral myocarditis was found in 30.9 percent of routine postmortem specimens using the immunofluorescent technique,[17] the incidence of clinically undetected Coxsackie viral heart disease is probably high. How many of these patients had active myocardial infection and how many merely had dormant viruses present from previous infections were not determined. When the hearts of 50 infants and children were examined at routine necropsy using similar methods, 29 were found to have interstitial myocarditis. Twelve of the 29 (41 percent) were found to be associated with Coxsackie B viral antigens.[16]

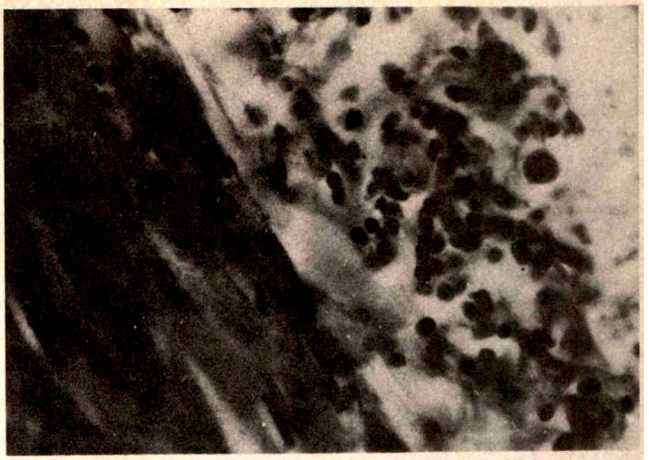

Figure 2. Photomicrograph showing pericarditis in a cynomolgus monkey following infection with Coxsackie virus B_4 (hematoxylin and eosin × 450, reduced by 11 percent.)

Experimental myocarditis: Numerous studies in experimental animals confirm the highly cardiotropic nature of Coxsackie viruses. All suckling mammals, including man, are highly susceptible to the virus.[5] Virus multiplication was found in the heart as well as other tissues of newborn mice[55] 1 day after inoculation with Coxsackie B virus (Connecticut-5 strain). Studies in mice using Coxsackie B_3 virus (Nancy strain) as the infective agent indicated that the myocardial damage seen in such infections is produced by viral multiplication within myocytes.[56] "Conditioning factors," such as roentgen irradiation, anoxia, steroids and various types of myocardial injury, increased susceptibility to infection and tissue injury by Coxsackie group B viruses.[57] Exercise produced similar results in adult mice inoculated with Coxsackie virus A9.[58]

In mice infected with Coxsackie virus B_4, ultrastructural changes of the myocardial cell were seen, which consisted of cellular shedding, membranous damage, vesicle complex formation, disappearance of Golgi body, nuclear shrinkage and densification of chromatin and an increase in ribosomal population.[59] These changes are similar to those observed in tissue cultures infected with virus.[60] In addition to myocardial cellular changes, damage to the myocardial capillaries occurred in mice infected with Coxsackie virus B_4[61] as well as nonspecific changes characteristic of cellular injury. The virus was located within the myocardium both by immunofluorescent technique[31] and by electron microscopy using ferritin-labeled antibodies.[62]

The production of Coxsackie viral myocarditis in adult mice without the use of conditioning factors,[58] as well as in young cynomolgus monkeys and chimpanzees, has been extremely interesting. Coxsackie virus B_4 obtained from the heart of an

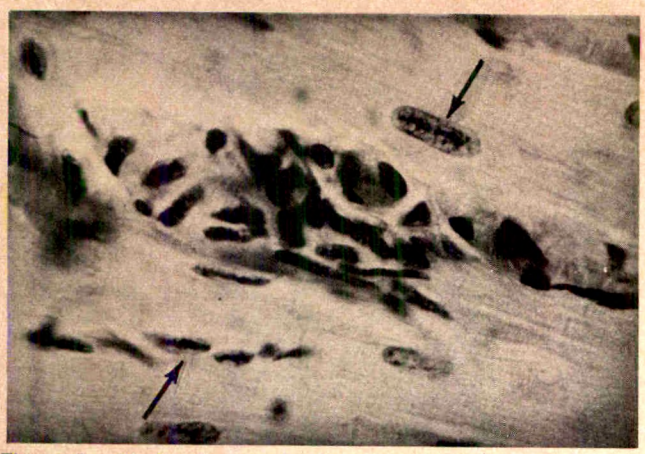

Figure 3. Photomicrograph of myocardium obtained from a cynomolgus monkey 185 days following intravenous inoculation with Coxsackie virus B_4 showing myocarditis and an Aschoff-like body with A-nitschkow myocytes (**arrows**). (Hematoxylin and eosin × 450, reduced by 12½ percent.)

infant who died of myocarditis[63] was administered intravenously to 9 healthy cynomolgus monkeys.[64] After infection, 8 monkeys had myocarditis and 6 had virus recultured from the heart. In another group of cynomolgus monkeys infected with Coxsackie B_4 virus, histologic lesions resembling those characteristic of "rheumatic fever" were seen[30] (Fig. 3). Thus, it has been clearly shown that the Coxsackie viruses produce active myocarditis in man and animals.

Influenzal Myocarditis

There can be little doubt that influenzal viral infection can produce clinically evident myocarditis and that influenzal myocarditis may occur as a complication of other types of heart disease.[65,66] In some instances the virus has been isolated from the myocardium.[67] We have recently seen a patient with ischemic heart disease who died after an illness compatible with influenza and in whom the virus was isolated from myocardial tissue (unpublished data).

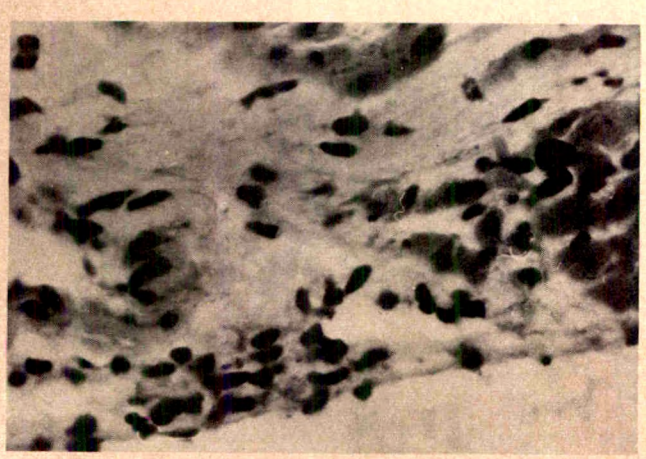

Figure 4. Photomicrograph showing inflammation of the mitral valve of a cynomolgus monkey 7 weeks after intravenous inoculation with Coxsackie virus B_4. (Hematoxylin and eosin × 450, reduced by 26 percent.)

Other Viral Causes of Myocarditis

Most viruses known to cause a clinical illness in man have at one time or another been shown to produce acute myocarditis.[1,2,5,22,35,48,68] Many of the viruses that have been reported as causing myocarditis in man are listed in Table I. In addition to the Coxsackie viruses, poliomyelitis virus and the other members of the picornavirus group are highly cardiotropic for man. However, the poliomyelitis vaccine has essentially eradicated poliomyelitis, so that it is no longer a major cardiovascular threat.

Possible Viral Causes of Cardiomyopathy

Viruses may play a primary etiologic or complicating role in the cardiomyopathies.[5,35,68–70] The precise mechanisms whereby viruses cause acute or chronic cardiomyopathy are not known. It has been suggested that the chronic disease may represent an old "burned-out" myocarditis.[9] Support for this concept is found in 2 recent reports. Of 42 adult patients with Coxsackie virus B myocarditis, 3 had residual cardiomegaly.[71] In another group of 22 similar patients, 5 had evidence of permanent myocardial damage.[72] Recurrence of "active" myocarditis was seen in 7 of the 22 patients. An immune mechanism responsible for continuing myocardial damage has been suggested[8] whereby the viral agent would alter the myocardial cell in such a fashion as to cause it to produce antibodies against itself. However, this mechanism for autoimmune reaction has not been definitely established. The possibility that certain "adjuvant-like" substances might play a role in an autoimmune phenomenon with resultant myocardial damage was also suggested. Obviously, studies of an etiologic role of viruses in patients with cardiomyopathy have been inconclusive.[9,73,74]

Postpartal heart disease: In certain cardiomyopathies, the role of viruses appears especially likely. For example, the postpartal state may, in some patients, be favorable for the initiation of viral diseases. At least 4 patients with postpartal heart disease secondary to Coxsackie viral infection have been described.[72] The concept that the pregnant and postpartal states may be more conducive to the development of viral heart disease is supported by the observation that pregnant mice are more susceptible to the encephalomyocarditis virus than nonpregnant mice.[75] Similar observations have been made following Coxsackie infection in pregnant mice (unpublished data). These concepts await thorough investigation.

Conditioning factors in cardiomyopathy: Toxic agents, such as alcohol, may serve as conditioning factors for viruses. Viral-like particles were found in the heart of a patient with alcoholic cardiomy-

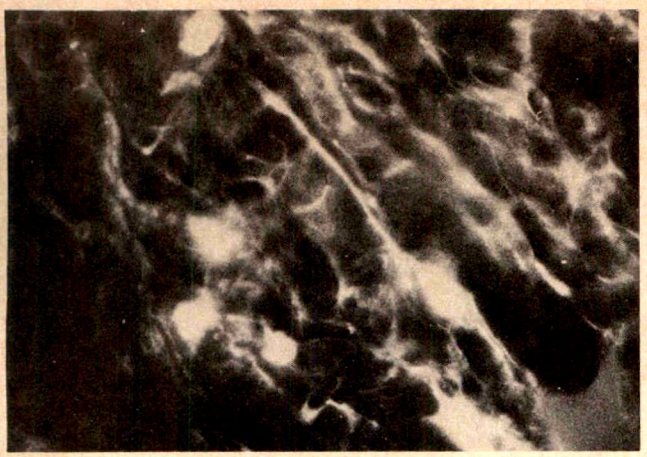

Figure 5. Photomicrograph of aortic valve of a cynomolgus monkey 162 days after intravenous inoculation with the virus, showing localization of Coxsackie virus B_4 antigen by the indirect immunofluorescent technique. (Hematoxylin and eosin × 450, reduced by 27 percent.)

Figure 6. Chronic mitral valvulitis secondary to Coxsackie virus B_4 infection. Mitral valve of a cynomolgus monkey 155 days following intravenous inoculation with Coxsackie virus B_4. The valve shows scarring of the leaflets and thickening and shortening of the chordae tendineae.

opathy.[76] Other conditioning factors include myocardial trauma, steroids, ionizing radiation, malnutrition, psychic stress, and other toxic and physical agents such as heavy metals, drugs, catecholamines, patent medicines and thermal stress. The activation of dormant or latent viruses by such conditioning factors in the continuing process of myocardial destruction should be considered.

Viral Endocarditis and Valvulitis

Viral Valvulitis

Whereas viral pericarditis and viral myocarditis have received some recognition among physicians and are readily acknowledged, the concept of viral valvulitis has not been readily accepted. This is difficult to understand. Why should viruses be expected to infect and injure only the pericardium and myocardium? Surely, the endocardium does not display any peculiar resistance to virus or bacteria. Not only has clinical evidence of viral valvulitis been observed,[77] but the production of endocarditis experimentally in animals by viruses provides definitive proof that viruses will damage the valves and mural endocardium. For example, Coxsackie B_4 virus produced acute valvulitis when administered to cynomolgus monkeys[78] (Fig. 4 and 5). Valvulitis was observed in the mongoose inoculated with encephalomyocarditis[79] and in rabbits inoculated with Virus III.[13]

Experimental chronic valvular lesions: Since acute valvulitis can be produced in experimental animals by viruses, it seems likely that chronic valvular lesions can also be produced in these animals when the acute lesions heal. Chronic studies in cynomolgus monkeys inoculated intravenously with Coxsackie B_4 virus support this concept.[78] In these experiments gross (Fig. 6) and microscopic valvular lesions occurred as long as 200 days after the initial inoculation. The lesions resembled those of "rheumatic heart disease" with aortic and mitral stenosis and insufficiency.[30] Both acute and chronic valvular lesions were seen in mice after inoculation with Coxsackie virus B_4.[80] In the latter studies the Coxsackie virus B_4 was recovered as late as 8 days after the experiments began. Electron microscopic examination of the endocardial tissue of mice inoculated with Coxsackie virus B_4 showed changes compatible with viral infection.[81] The occurrence of valvulitis after inoculation of mice with adenovirus, with typical electron microscopic changes, has also been reported.[82,83]

The exact incidence of viral valvulitis in man is not known. However, Coxsackie viral antigen was located by the immunofluorescent technique in the valves of 3 of 55 patients (Fig. 7) randomly selected at routine autopsy.[17] Thus, it seems that Coxsackie virus B_4 can produce valvulitis in man.

Figure 7. Photomicrograph of a mitral valve leaflet of a 3-day-old infant showing presence of Coxsackie virus B antigen by the immunofluorescent technique. Light microscopy showed diffuse myocarditis. (Hematoxylin and eosin × 450, reduced by 32 percent.)

"Rheumatic" Heart Disease

Although "rheumatic" heart disease involves all layers of the heart, it is too frequently identified only with chronic valvular heart disease in man. In fact, the terms are often used interchangeably today. Because rheumatic fever is considered by many to be secondary to a preceding streptococcal infection,[84] the clinician is forced to consider all chronic, acquired valvular heart disease in man as being induced by streptococci. Yet, a third to a half of patients with "rheumatic" heart disease do not present a definite history of a preceding streptococcal infection.

Mixed streptococcal and viral infection: A critical review of the evidence for a streptococcal origin for chronic valvular heart disease suggests that many instances of valvular heart disease are produced by viruses.[12] Streptococci certainly could act as a conditioning factor for cardiotropic viruses. The incidence and severity of Coxsackie virus B_4 myocarditis were increased when mice were given streptococci as well as the virus (unpublished data). An immunosuppressant effect of group A streptococci has also been reported.[85] Thus, in some instances, the streptococcus might act as a conditioning factor or might activate dormant or latent or slow viruses located in the heart. These latter thoughts may be extremely important since certain viruses known to be cardiotropic for man, such as the Coxsackie viruses, produce a significant amount of upper respiratory tract disease with pharyngitis in man.[86] These viruses often go undetected or unidentified.[87] It should be remembered that mixed viral and bacterial infections frequently occur.[11]

Prevention and Treatment of Viral Heart Disease

Vaccines for prevention: The use of vaccines is currently the primary means of prevention of viral illnesses. The development of the rubella vaccine should cause a reduction in the incidence of congenital heart disease. Because Coxsackie viruses have also been implicated as causes of congenital heart disease,[15] the need for a Coxsackie vaccine has already been considered. Whether or not a vaccine would be effective in the prevention of heart disease due to viruses in the adult population will depend on epidemiologic studies. Some vaccines produce a lasting immunity, whereas others produce little or no immunity or immunity for only a short time. It should still be considered prudent to immunize, when possible, patients with any type of heart disease against viruses that are known to cause complications, such as the influenza virus. An effective vaccine is needed for all highly cardiotropic viruses.

General measures in acute phase: The treatment of acute viral heart disease is, in most instances, symptomatic. There are no effective viral antibiotic agents available to date. Pain, a frequent symptom in acute viral pericarditis, may respond to simple analgesic agents. Care must be taken to avoid the use of anticoagulant agents in patients with acute viral pericarditis since hemopericardium may result.[88] Arrhythmias are common in all types of viral heart disease and generally respond to conventional therapy. Bacterial antibiotic drugs may be used prophylactically in viral infections to prevent complicating bacterial infections. They are surely indicated once bacterial infections develop.

Patients with mild acute viral heart disease should be kept at bed rest until the viral infection has definitely subsided. The effect of exercise and fatigue on increasing tissue damage from viral infections has been noted.[89,90] Patients with severe myocarditis who have residual cardiomegaly should probably be kept at bed rest for 6 months to a year depending on the clinical response in order to permit adequate healing and to allow the heart to return to normal size. The reasons for and response to prolonged bed rest in the management of heart muscle disease have been discussed in detail elsewhere.[91,92]

Digitalis and diuretic agents: In patients with severe myocarditis and cardiac decompensation, digitalis should be used cautiously to avoid the occurrence of dangerous arrhythmias. Orally administered diuretic agents should be used as little as possible because of their kaliuretic action and, in turn, tendency to produce arrhythmias, even fatal ones, especially when used in conjunction with digitalis. Mercurial diuretic agents, which are not kaliuretic and therefore cause less trouble with arrhythmias, are preferred.

Corticosteroids: The value of steroids in the treatment of acute viral heart disease is not established. Theoretically, there is some danger in giving steroids early in the course of a viral illness.[93,94] Steroids can potentiate viral infections. However, it has been pointed out that heart disease can occur after the virus has already been widely disseminated and an antigen-antibody type of reaction established and that this reaction might be controlled to some degree by steroid therapy.[95] Nevertheless, the clinician must be certain he is not concerned with a viral infection itself when he prescribes steroids. As is often the case in clinical medicine, some clinicians have had success with this type of therapy,[96] whereas others have not.[72]

Comments

Possibilities for the future treatment of viral diseases, both acute and chronic, are exciting. The possible role of interferon, interferon-inducers, viricidal drugs, new viral vaccines and molecular manipulations in the treatment of viral disease are now being explored. Success with some of these

is certain to be obtained in the near future.

From this brief review it is evident that, although much data have been collected, we know very little about the incidence of viral heart disease or the innumerable ways in which viruses can damage the heart. It is clear that, clinically at least, progress in the diagnosis and management of viral diseases of all types will be hampered until adequate viral laboratory facilities for the diagnosis of viral diseases are available on a nationwide basis. Such facilities constitute one of the great needs in clinical medicine. In addition, special hospitals and hospital facilities for patients with heart disease are needed where such patients can be adequately studied and properly hospitalized for as long as necessary.

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Seminar on
Clinical Application of Techniques to Measure Blood Flow in Man. Part II
ALBERTO BENCHIMOL, MD, FACC, Guest Editor

Measurement of Blood Flow by Thermodilution

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In thermodilution a known change in heat content of the blood is induced at one point of the circulation and the resultant change in temperature detected at a point downstream. When cardiac output is measured, a bolus of cool liquid is injected into the upper right atrium and the temperature change detected in the pulmonary artery. When flow in single blood vessels is measured, the distance between the site of injection and the site of detection is small; therefore, mixing must be attained by the kinetic energy of the injectate. The continuous constant rate injection technique is most suitable for measurement of venous flow. Since the blood flow in arteries can be markedly and unpredictably altered by the injection or the injectate, this technique is not suitable to measure flow in arteries. Measurement of venous flow by the bolus injection technique is tedious and time-consuming because of the complex formula. Minimal recirculation, simple and accurate calibration, intravascular detection of temperature and simple equipment are the advantages of the thermodilution technique.

Thermodilution was introduced as a method for the measurement of blood flow by Fegler in 1954.[1] The idea that heat can serve as indicator was received with skepticism which only in recent years appears to have been overcome. The objective of this communication is to define the principles on which the measurement of cardiac output and blood flow in single vessels with the thermodilution method is based, its limitations and potentials and to present certain modifications of technique which enhance practical application.

Thermodilution represents an application of the indicator dilution principle in which a known change in the heat content of the blood is induced at one point of the circulation and the resulting change in temperature detected at a point downstream. Heat can be either added, using various intravascular heating devices,[2,3] or abstracted, usually by injecting into the blood stream a non-toxic mass miscible with the blood and at a lower temperature. The latter is similar to the dye dilution method from the technical point of view and is also most commonly used.

Measurement of Cardiac Output by Thermodilution

Principle: A bolus of a cool liquid is rapidly injected into the superior vena cava or the upper part of the right atrium and the resultant change in temperature detected in the pulmonary artery or in the aorta. A temperature-time curve is recorded which is similar in configuration to a dye-dilution curve except for the absence of recirculation peaks and a more protracted downslope. As in other indicator-dilution techniques

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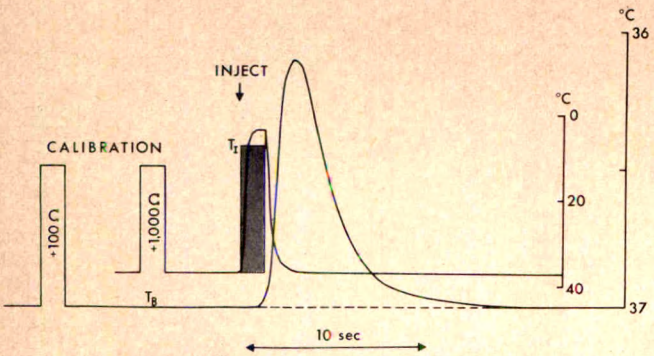

Figure 1. Diagrammatic representation of a tracing during measurement of cardiac output by thermodilution. After injection of a cold bolus ("inject") a temperature-time curve is recorded first by the thermistor in the lumen of the catheter. From the area under the build-up (cooling) part of the curve (estimated by planimetry), the mean temperature of the injectate (T_I) can be determined. The temperature-time curve recorded by the thermistor in the pulmonary artery has a 1 to 2 second appearance time. T_B = temperature of the blood in the pulmonary artery. Calibrating resistances = +1,000 ohms for the injectate thermistor, +100 ohms for the thermistor in the pulmonary artery.

uniform mixing of the indicator with blood over the whole vascular cross-section is a basic assumption for the validity of the method. From the change in the heat content of the blood, induced by the injection of the cool bolus, and from the temperature-time curve the cardiac output can be calculated.

The formula for calculation of cardiac output is derived on the basis of the fact that in the mixture of blood and the injectate the heat gained by the injectate is equal to the heat lost by the blood, assuming that no indicator was lost from the system between the site of injection and the site of detection by heat conduction or energy conversion.[4,5]

$$V_B = \frac{V_I \times S_I \times C_I \times (T_B - T_I) \times 60}{S_B \times C_B \int_0^\infty \Delta T_B(t)dt} \quad (1)$$

where

V_B = cardiac output in ml/60 sec;
V_I = volume of the injectate in ml;
S_I, S_B = specific gravity of indicator and blood, respectively;
C_I, C_B = specific heat of indicator and blood, respectively;
T_B, T_I = temperature of blood and indicator, respectively;
$\int_0^\infty \Delta T_B(t)dt$ = area (A) under the temperature time curve in °C × sec

The specific gravity of the blood, dextrose solution and saline is 1.045, 1.018 and 1.005, the corresponding specific heats 0.87, 0.965 and 0.997, respectively. Although the specific gravity of the blood changes with the hematocrit, the product $S_B \times C_B$ remains virtually constant, because the specific heat of the blood changes proportionately in the opposite direction.[4]

$(S_I \times C_I)/(S_B \times C_B) = 1.08$, when isotonic saline or 5 percent solution of dextrose is injected.

Equation 1 can be then written in the following form:

$$V_B = \frac{V_I \times (T_B - T_I) \times 60 \times 1.08}{A} \quad (2)$$

Quantitation of indicator represents a special problem connected with the use of heat as indicator. When the cool fluid is injected through an intravascular catheter, the temperature of the injectate constantly changes as it passes through the lumen because of heat exchange with the wall of the catheter and the surrounding blood. The temperature of the injectate, as used in the formula for calculation of cardiac output, is the mean value of the continuously changing temperature at the point of entry into the blood stream. This value can be determined by recording with a fast response sensor the time course of the temperature of the injectate near the injection orifice; assuming a virtually steady injection rate, the mean temperature determined for the duration of the injection from the temperature-time curve will give the mean effective temperature of the indicator (Fig. 1). Practical considerations in catheter construction favor elimination of the direct measurement of the temperature of the indicator. Two ways have been used to correct for the loss of indicator during injection: (1) Calorimetric determination of the heat transfer to the injectate under conditions simulating the experiment,[6] and (2) measurement in vitro of the temperature of the injectate leaving the catheter under conditions simulating the experiment. A factor can be derived that will correct for the amount of indicator lost during passage through the injection lumen. Since the loss of indicator is caused by a decrease in the temperature difference between the blood and indicator, the correction factor (C) can be expressed as

$$C = \frac{T_B - T_{IL}}{T_B - T_I}$$

where T_{IL} is the mean temperature of the injectate leaving the catheter, and T_I is the temperature of the injectate measured immediately before the injection.

Measurements with a triple lumen flow-directed thermodilution catheter (Edwards Laboratory, Santa Ana, Calif.) (made from polyvinyl chloride) showed that the correction factor is virtually not affected by the temperature of the surrounding blood (in the range from 35 to 39 C), by the rate of injection (in the range from 10 ml/2 sec to 10 ml/4 sec) and only slightly (±1½ percent) when the length of the intravascular segment is changed from 35 to 25 or 45 cm. The value for C in these measurements was 0.825 ± 0.014 (mean ± standard deviation). The temperature of the injectate measured immediately before the injection (T_I) is used in the formula for estimation of cardiac output and the factor (C) is included in the numerator for correction.

The injectate remaining in the lumen of the catheter may cause additional cooling of the blood by conduction across the wall of the catheter. Although this effect might be negligible, depending on the volume of the dead space of the catheter in contact with the circulating blood, the thermal conductivity of the catheter and the ratio of the volume of dead space to the total injected volume, it may delay the return of the downslope to the base line. We therefore recommend withdrawal of the residual injectate immediately after the injection.

Heat exchange between the site of injection and the site of detection: The validity of the method is based on the assumption that the amount of indicator lost between the site of injection and the site of detection is negligible. As the mixture of blood and injectate travels from the superior vena cava to the pulmonary artery, the wall of the vessels and heart chambers is first cooled; as the temperature of the blood rises again, the walls are rewarmed. This bidirectional heat exchange between the blood and the vessel walls leads to distortion of the shape of the temperature-time curve: reduction of the height and prolongation of the rewarming part. The total area of the temperature-time curve is not reduced, since cardiac output calculated from the thermodilution curves showed no systematic deviation from values obtained by other accepted methods whether the temperature was measured in the pulmonary artery[7–14] or in the proximal aorta.[1,15] Comparison of cardiac outputs determined simultaneously by the dye (CO_{DYE}) and thermodilution (CO_{TD}) methods in human subjects in this laboratory[14] gave the following results:

Equation of the regression line:

$$CO_{TD} = 0.96\ CO_{DYE} + 0.2$$

Correlation coefficient $r = 0.960$

$P < 0.001$

However, when the pulmonary capillaries are surrounded with significant amounts of fluid, as in left heart failure or pulmonary edema of whatever origin, a significant unidirectional heat transfer between the lungs and the blood-indicator mixture will occur. Under those conditions, the aorta cannot be used as the sampling site.

Recirculation of indicator: The ratio of surface area to volume increases with decreasing vessel diameter. The rate of heat exchange between the blood and the surrounding tissues is therefore maximal in the capillaries. By heat and fluid exchange over the large surface area of the capillaries of the systemic circulation, the blood is rewarmed virtually to its preinjection temperature. Recirculation is therefore very slight. In addition, when the site of detection is in the pulmonary artery, the distance from the site of injection is usually short enough to permit the primary curve to be completed before recirculation can occur.

Fluctuation of blood temperature: The temperature of the blood in the right atrium, right ventricle and pulmonary artery shows cyclic changes synchronous with respiration, probably caused by temperature differences in various venous beds and by respiratory changes in their relative contribution to the venous return.[14–17] The fluctuation in the pulmonary artery is about 0.01 to 0.02 C, but it can be greatly increased in the presence of abnormalities in respiratory pattern (for example, Cheyne-Stokes respiration). It represents a physiologic "noise" and requires augmentation of the "signal." This can be achieved by increasing the rate of indicator input by (1) increasing the injection rate and (2) lowering the temperature of the injectate. In this laboratory a satisfactory "signal to noise ratio" is obtained by injecting 10 ml of 5 percent dextrose solution at preinjection temperatures of 0 to 5 C within 2 to 3 seconds.

Measurement of temperature: Thermistors are used most frequently because of their high temperature coefficient (3.5 to 4 percent change in resistance per 1 C change in temperature). Their temperature-resistance characteristic is logarithmic. However, over the small range in which the temperature of the blood in the pulmonary artery changes during the determination of cardiac output (usually less than 1 C), the characteristic can be considered linear. A fixed resistance of appropriate value in parallel with the thermistor can be used to linearize the thermistor characteristic over a wide range of temperature.

The resistance of the thermistor is measured with a Wheatstone bridge, into which the thermistor is incorporated as one arm. The voltage across the thermistor is kept low (below 100 mv) to avoid sensitivity to changes in the velocity of flow without changes in temperature. The bridge is balanced before each measurement. The off-balance output resulting from changes in temperature is amplified by a direct-current amplifier and recorded. The galvanometer deflection is calibrated by adding a resistance in series with the thermistor. The change in temperature represented by the calibrating resistance is determined from the temperature-resistance characteristic of the thermistor.

The current flowing through the thermistor is kept low (about 20 μamp). Nevertheless, from the standpoint of patient safety it is advisable to check the electrical insulation of the thermistor before each application. The insulation can be tested in the following way: (1) Connect 1 lead from the thermistor to 1 pole of a variable d-c voltage source in series with a sensitive (e.g., 1μamp full scale) microammeter. (2) Immerse the second pole of the voltage source into saline solution. (3) With the voltage set to 0 immerse into the saline the distal part of the catheter carrying the thermistor. (4) Raise the voltage slowly. If no deflection is noted on the meter at any level up to 100 v, the insulation can be considered adequate.

Clinical usefulness: Although the use of heat as indicator has its limitations and special problems, requiring cautious attention in its application, it has important practical advantages in comparison with the dye indicator. It does not require arterial puncture, since no blood is withdrawn from the arterial system for measurement and calibration. This facilitates studies at the bedside in simplicity of performance and acceptance by the patient. The calibration of the thermodilution curves is simple and accurate and can be done for each measurement. Two or three measurements of cardiac output can be carried out in 1 minute. The equipment is simple and inexpensive.

Measurement of Flow in Single Blood Vessels by Thermodilution (Local Thermodilution)

Since thermistors and thermocouples are small enough to be mounted on catheters and so inserted into vessels of relatively small diameter, thermodilution, from a technical point of view, is particularly suitable for measuring blood flow in single vessels.

Principle: A change in the heat content of the blood is induced at 1 point in the vessel and the resul-

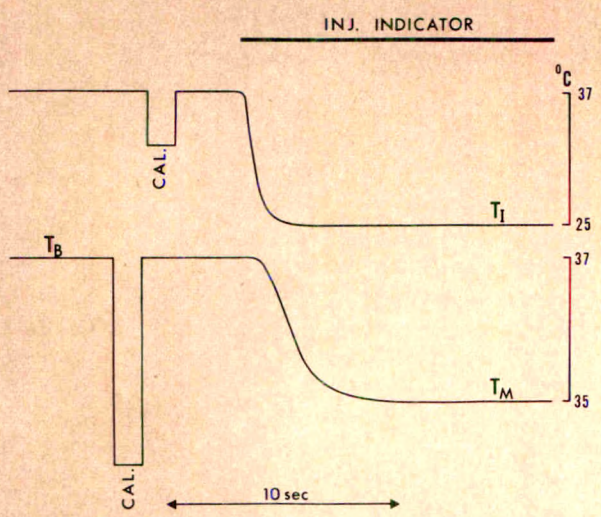

Figure 2. Diagrammatic representation of a tracing obtained during measurement of blood flow by continuous constant injection thermodilution. T_B = temperature of blood, T_I = effective temperature of the injectate; T_M = temperature of the mixture of blood and injectate.

tant change in the temperature detected at a point downstream. Uniform temperature over the cross section of the vessel at the point of detection is a basic requirement for the accurate measurement of flow. When cardiac output is measured, mixing is achieved by the pumping action of the heart. However, in local thermodilution mixing is attained by the kinetic energy of the injectate which must be sufficient to induce turbulence over the whole cross section of the vessel. When a heating device is used, a special stirrer must be applied for uniform distribution.[3] The thermal indicator can be introduced either as a single, nearly instantaneous injection, or by continuous constant rate injection. Because the distance between the site of injection and the site of detection is short, the effect of the injection on the rate of blood flow must be taken into account when formulae for computation of blood flow are derived.

Measurement of Blood Flow in Veins

Continuous injection: When the indicator is introduced by continuous constant rate injection, after some delay a steady state is reached in which the amount of indicator leaving the mixing volume in a unit time interval is equal to the amount entering the mixing volume during the same time interval (Fig. 2). In contrast to arteries the blood flow in veins upstream to the site of injection is not reduced during the injection because in veins the resistance upstream is much higher than downstream. The injected volume (V_I) mixes therefore with an unaltered volume of blood (V_B). Since the heat lost by the blood during the process of mixing is equal to the heat gained by the injectate, assuming that no significant heat has been lost from the system, the following heat balance equation can be written:

$$V_B \times S_B \times C_B \times (T_B - T_M) = \text{(Heat lost by blood)}$$

$$V_I \times S_I \times C_I \times (T_M - T_I) \quad (1)$$
(Heat gained by injectate)

where

T_M = temperature of the mixture of blood and indicator, after a steady state has been reached.

$T_M - T_I$ can be written as $(T_B - T_I) - (T_B - T_M)$

The formula for calculation of flow in veins by continuous thermodilution is therefore:

$$V_B = V_I \times \frac{S_I \times C_I}{S_B \times C_B} \times \left(\frac{T_B - T_I}{T_B - T_M} - 1\right) \text{ml} \quad (2)$$

or, if isotonic dextrose or saline is used,

$$V_B = V_I \times 1.08 \times \left(\frac{T_B - T_I}{T_B - T_M} - 1\right)$$

Rate of injection of indicator: The kinetic energy of the injectate must be high enough to induce turbulence over the whole cross section of the vessel. The conditions of mixing have not been precisely mathematically defined; however, it is known that the kinetic energy necessary for good mixing is directly related to the velocity of blood and to the diameter of the vessel. The spatial orientation of the stream of indicator in relation to the direction of the blood stream and the vessel wall is an additional factor affecting the degree of mixing.

Measurement of phasic flow: The response time of the continuous thermodilution method depends on the time constant of the temperature sensing and recording system and the time constant of the mixing volume (= mixing volume [ml]/total flow of blood and indicator [ml/sec]).[18]

The time constant of the mixing volume is usually higher than the time constant of the temperature-sensing device which can be kept below 0.1 second; the time constant of the method (the time interval necessary to record 63 percent of the maximal change in T_M after a square wave change in blood flow) is therefore mostly determined by the time constant of the mixing volume, which is usually between 0.5 and 1 second. The method can measure phasic flow with reasonable accuracy if the cycle length of the change in flow is 1.5 to 3 seconds or more.

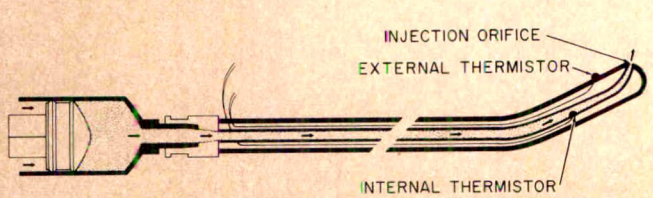

Figure 3. Diagrammatic representation of a catheter for measurement of flow in single blood vessels. The cool fluid is injected through a special tube thermally insulated from the external catheter by a space of air. The temperature of the injectate is measured by the internal thermistor; the temperature of the blood and of the mixture of blood and injectate by the external thermistor.

Thermodilution catheters: Catheters for measuring blood flow by the continuous thermodilution method have 2 thermistors (Fig. 3): 1 placed on the outside for determination of T_B and T_M, and 1 placed in the lumen for determination of T_I. Thermal insulation of the injectate from the blood will minimize the heat transfer and also the pos-

sible error from this heat transfer. Catheters have been constructed which can be inserted percutaneously to measure blood flow in the internal jugular, popliteal and iliac veins in human subjects.[19–23] Somewhat larger catheters are employed for estimation of blood flow in the coronary sinus and great cardiac vein.[24]

Accuracy: Comparison with direct methods in model and in vivo studies demonstrated high accuracy of the continuous constant infusion thermodilution method.[9,22,24–26] Comparison of blood flow estimated by the continuous thermodilution method (Y) in the coronary sinus in dogs with timed collections of blood *(X) in this laboratory*[24] gave the following results:

Equation of the regression line:	$Y = 0.99X + 0.3$
Correlation coefficient	$r = 0.995$
	$P < 0.001$

Measurement of blood flow in veins by the single injection method: If a bolus of cool fluid is injected at 1 point of a vein, a temperature-time curve is recorded downstream, similar to curves recorded during measurement of cardiac output. However, the computation of blood flow is complicated by the fact that part of the temperature-time curve is inscribed, when the flow downstream to the site of injection is increased by a portion of the injectate. The second part of the curve is inscribed when the flow rate has again returned to its preinjection level. A complex formula for the calculation of flow was derived by solution of a pair of heat-balance equations, using areas under the 2 parts of the curve.[4] The need to measure 2 areas is a limiting factor in the use of the single injection technique.

Measurement of Blood Flow by Thermodilution in Arteries

Continuous injection: The applicability of thermodilution (and other indicator-dilution methods) for the measurement of blood flow in arteries is seriously limited by alterations of blood flow during the injection of cool fluid. (1) Due to the high downstream resistance in arteries,[4] the kinetic energy of the injection causes a reduction in the blood flow, with a secondary dilatory response from the arterioles. (2) The injection may damage some erythrocytes and by liberation of vasoactive intracellular substances cause arteriolar dilatation and increase in the measured blood flow.[27] Therefore, the continuous injection method does not appear to be suitable for the measurement of blood flow in peripheral arteries. However, this is not the case in the thoracic aorta, where continuous injection of dye was successfully used for the measurement of blood flow.[28,29]

Measurement of arterial flow by the single injection method: Since the distance between the site of injection and the site of detection is short, in case of a bolus injection a temperature-time curve can be inscribed before the effects of the injection on the arterioles become manifest. If the kinetic energy of the injectate is not excessive,[4] the injectate will displace an equal volume of blood; that is, the total flow downstream to the site of injection will remain unchanged during the injection. From the heat balance equation, and with respect to the effect of the injection on blood flow, a formula for estimation of arterial blood flow can be derived which is essentially identical with that used for estimation of cardiac output. The single injection method has its theoretical limitations since it requires the assumption of a constant flow[30,31]; however, comparative measurements showed good agreement with direct methods.[4,32]

Conclusion

As may be apparent from the preceding discussion, the usefulness of the thermodilution method lies first of all in the determination of cardiac output and in the measurement of blood flow in veins. The progress in both areas has been significant in recent years, proving the correctness of Hosie's prediction when he wrote in his excellent review in 1962[5] that thermodilution "will continue to receive the attention which its simplicity and elegance merit and that with further improvement and verification of its usefulness the modest claims first made for it will be upheld."

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Cohnheim on Inflammation—I

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The great classic of the literature on inflammation is the essay by Julius Cohnheim (1839–84), *Ueber Entzündung und Eiterung (On Inflammation and Suppuration)*.[1] Although Cohnheim had been preceded by at least two observers—William Addison[2,3] and Augustus Volney Waller[4,5]—in the description of inflammatory vasodilatation and diapedesis, the earlier researches were far outdone by the amplitude and richness of the new German masterwork.

Cohnheim began by studying artificial inflammation in the avascular cornea of the frog. For this purpose he introduced the use of staining with gold chloride. He found that although innumerable "pus corpuscles" appeared, the epithelial cells of the cornea retained the normal location and arrangement. Hence, pus was not derived from corneal epithelium.

Two possibilities remained. Either the pus corpuscles were derived from wandering corneal elements which resemble "lymph bodies" (leukocytes) or they were immigrants into the cornea. To decide this, Cohnheim instituted a new series of experiments. He found that in simple keratitis, whether produced by means of a silver nitrate pencil or by a thread drawn through the eye, the inflammatory reaction constantly began at the *margins* of the cornea and advanced to the center. He explained this, correctly, by pointing out that the largest blood vessels are situated at the periphery.

If aniline blue was dropped into the conjunctival sac of a rabbit and the cornea was then cauterized, the leukocytes contained no blue granules. These leukocytes could have come only from the lymphatics or the blood vessels. If dye was instilled into the lymph sac of a frog, none appeared in the intact cornea. If dye was instilled into the lymph sac and the cornea was then injured, dye appeared in some of the leukocytes found in the inflamed area. This showed that at least some of the pus corpuscles came from elsewhere than the eye. When dye was injected into the aortas of a frog and the cornea was injured subsequently, the leukocytes in the cornea were found to contain dye. Hence, some pus corpuscles in the inflamed cornea had been undyed blood corpuscles previously and had entered the cornea by way of the blood vessels.

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Having found that it would be impossible to make further progress by means of an avascular structure such as the cornea, Cohnheim now turned to study inflammation in the mesentery of the live frog. The following excerpts contain the crucial observations that he made during this part of the investigation.

Excerpts from Cohnheim

The first thing that happens is widening of the arteries. Immediately after exposure of the mesentery—unless perchance a preexistent constriction can be observed*—the dilatation of the arteries usually begins; it can be very distinct after as short a time as 10 to 15 minutes. From that time on it increases steadily, with at most very small and brief intermissions and remissions. After one to two hours it has usually reached its maximum, at which it maintains itself during the entire remainder of the process, or else it diminishes by at most a few hundredths of a millimeter. The total effect of this widening can reach a very high degree. Nothing is more frequent than to see an artery having a diameter of 0.14 [mm.] increase to 0.22, and one of 0.15 go to 0.24. In an artery that measured 0.15 at the beginning I measured the width at 0.31 after 45 minutes, and in another that was 0.14 I found 0.35 mm. within an hour. An artery can expand to twice its original diameter. One thing must be added. Whereas at the beginning all the arteries are extended straight or run their course with only slight inflection, in the exposed mesentery many of them constantly develop very marked tortuosity and even though this depends only on elongation of the vessel, it can be understood how much the capacity of a dilated and simultaneously contorted vessel has increased. Moreover the widening of the arterial vessels, so far as they are exposed, is usually uniform despite the extension and tortuosity of their course. Only in isolated instances on checking over a preparation does one suddenly come upon a place so narrow that the lumen is only perhaps one third of what it is immediately behind this point. Just before this (i.e. toward the heart), there is almost always a similarly circumscribed place where the artery in direct contrast is dilated to an unusual degree, up to about twice the size of the section encountered immediately before. I cannot state what causes these irregularities, which often develop before one's eyes and with no perceptible provocation. They can last for hours. We shall have to return to them, since anomalous and highly instructive conditions can develop at such places.

The dilatation of the arteries is followed by a similar but very much slower occurrence in the veins. Regularly in the course of the process there is a stage in which the arteries greatly exceed the veins in width.

* Footnote omitted [SJ]

However what is lacking here in the speed of the process is more than compensated by magnitude and extent, and after a time the original proportionate relation always comes close to being reestablished. For example I find in my notes that a vein originally measuring 0.16 mm. increased to 0.24 mm. in 3 hours; another of 0.17 increased to 0.29; one of 0.13 increased to 0.28 in four hours, and one of 0.21 went to 0.44 mm. As can be seen, the original lumen can increase to double or more. At the same time in the veins, which are much more extensible than the arteries, sinuosities and curvatures are never seen to develop. I also do not recall having seen partial constrictions and dilatations, or at least not approaching the way they occur in arteries. As for the condition of the walls of the dilated vessels, the one difference from their normal appearance is that they seem a little thinner. Apart from this, after as well as before [inflammation], they present on optical longitudinal section a tissue of longitudinal fibers, in the arteries just as in the veins, but at most a little denser. Finally the capillaries and the changes that occur in them are to be considered together in a later paragraph.

At the same time that the dilatation of the vessels is developing, the speed of the blood within them is also undergoing changes, predominantly of variable character. In some vessels, both arteries and veins, a retardation of the blood current takes onset right from the beginning, together with progressive dilatation. In other vessels there is no change in the speed. In still others the observer merely thinks he observes acceleration, but this for obvious reasons is difficult to establish with certainty. But even more striking variations appear. In a vessel in which the blood current has already slowed appreciably, one may see *de novo* a considerable increase in speed unaccompanied by perceptible narrowing of the lumen. Nevertheless, however variable these conditions may be at the beginning, always and without exception, as soon as the vasodilatation has continued for a while—perhaps one or two hours—a decrease of the speed of the current sets in. Microscopically this slowing of the stream is manifested by the fact that thenceforth it becomes possible to distinguish the outlines of the individual blood corpuscles without difficulty, usually in the arteries and quite certainly in the veins, where the speed of the current was small even at the outset. Now the optical effect of the arterial pulsation also becomes much more evident. When the observer fixates persistently on one place in an artery, it appears as if the mass of blood propelled by the previous wave would now flow forward gently, until suddenly a new and stronger impulse seizes it and irretrievably carries it away.

One thing additional has changed: the bloodstream has lost its axial character. No longer does one see on both sides of the red blood column a colorless layer of plasma devoid of corpuscles, but the mass of blood fills the entire lumen of the vessel and the corpuscles at every place flow over the inner border of the vessel wall. In the arteries it is unmistakable that the colorless corpuscles make for the wall of the vessel. At the apparently outflowing wave, at the instant of greatest retardation of the blood current it is seen that the white blood corpuscles in the periphery of the entire column of blood are rolling over the wall of the vessel, as if they would come to rest there if the new wave did not drive them forward mercilessly . . .

[In the veins] a very characteristic condition immediately begins to develop, slowly, under the eye of the observer. The peripheral zone of the blood stream, the original plasma layer, becomes filled with innumerable colorless blood corpuscles. Single white corpuscles push into the field of vision in the direction of the capillaries in slow and occasionally somewhat retrograde movement. Immediately they come to rest at some point along the wall of the vessel, either persistently or perhaps only after a certain time, after they have been driven forward over an additional short distance. The number of cells that accumulate in the marginal zone becomes constantly greater. To these a few more are added here and there which have been thrust forward from the capillaries. These cells come into view from the central blood stream and immediately settle themselves at the wall. The final effect of this process is that after a shorter or longer time the entire marginal zone of the vessel is filled with colorless corpuscles, so that optical longitudinal section shows a single almost unbroken row of spherical white blood cells along the inner border of the wall of the vessel, while on raising the tube [of the microscope] if one focuses on the upper wall of the vessel, a sort of pavement of densely arranged colorless cells overlies the wall. It is so to speak a single-layered but complete rampart of stationary white corpuscles investing the vessel in its entire periphery. When, as occasionally happens—and this is not unusual—a gap is torn in this wall because a few of the corpuscles are seized by the blood stream and pulled away, the space is filled immediately by oncoming followers. Within the wall, however, the red column of blood flows with even speed, without even one colored corpuscle becoming separated at any time from contact with the others; and I know no contrast that could be more distinct than that between the continuously streaming central red column and the quiescent marginal layer of colorless corpuscles.

However, this condition does not last long and the observing eye becomes attracted by a very unexpected occurrence. At the outer border of the wall of the vein there arise a few small colorless button-shaped elevations, just as if the vessel wall itself pushed forth gibbous excrescences. These excrescences slowly and very gradually become larger. After a while a hemisphere about half the size of a white blood corpuscle appears to lie on the outside of the vessel. Later the hemisphere changes into a piriform structure that has its dilated end directed away from the vessel and its pointed end rooted in the vessel wall. Then delicate processes and prongs radiate from the periphery of the piriform corpuscle, and although up to this time its contour has been more or less rounded, it now assumes highly diverse forms. Above all, however, the main mass of the corpuscle, the swollen irregular end, separates itself more and more from the wall of the vessel; the sharpened [proximal] end gradually draws itself out into a long thin stalk that I have seen attain the length of 0.05 or even 0.07 mm. Finally this stalk becomes separated from the point on the wall where it had been attached, and we now have before us a colorless somewhat shiny contractile corpuscle with a few short processes and one very long one. The size of the corpuscle corresponds completely with that of a white blood corpuscle. Not rarely, despite any change in shape in the fresh condition and at any rate after treatment with reagents, one or more nuclei are observable in it. Consequently it is in no way distinguishable from a colorless blood corpuscle.

It requires no small degree of self-control and dedicated concentration to keep the gaze constantly on this point. During the protracted time that elapses from the first gibbous protrusion until the separation of the corpuscle—this process can extend itself over a period of more than two hours and it often runs much more rapidly—at many other places along the vessel wall a large number of other colorless corpuscles have protruded themselves and when one has allowed the eye to pass for an instant over the entire portion of the vein that lies in the field of vision, one simultaneously catches sight of all the stages that had previously been seen developing in a single corpuscle. Smaller and somewhat larger gibbous excrescences, piriform elements with shorter or longer stalks rooted in the vessel wall—all this one sees simultaneously in varying amounts. Some of the corpuscles that have long stalks are entirely quiescent; others go through a very special performance and make small, rocking, pendulous movements with the dilated ends which constitute their main bodily masses, while the stalk remains attached. Gradually the number of protruding colorless corpuscles becomes larger and larger. About three or four hours after the first swelling is noticeable on the outer side of the vein, the vessel is surrounded by a single but dense ring of these corpuscles, which are set up around it like fixed pickets. A few hours later it is not merely a simple layer of colorless bodies that surrounds the vessel but a real forest. A swarm is spread out on all sides; four, six, and more rows of irregular but thickly placed corpuscles follow one another from within outward. The corpuscles in the innermost rows are attached to the vessel wall by longer or shorter stalks in the manner already described; those of the nearest rows in an outward direction are still very distinctly characterized by their long drawn out processes directed toward the veins; those in the outermost rows become constantly shorter, so that finally one sees nothing else than the usual changing forms of contractile corpuscles of blood or pus. In a few hours, I said; but according to what I have previously stated, this is to be understood cum grano salis. In the entire process of inflammation there is no phase that runs more irregularly than this extrusion of colorless corpuscles at the outer periphery of veins. While in certain individuals, especially of [*Rana*] *temporaria,* I saw this as early as three to four hours after exposure of the mesentery, in other specimens 12 or even 15 hours and more elapsed before even faint beginnings were evident. This variation appears not only in different individuals; even in one and the same frog a particular vein can be kept under observation for one or two hours without the contour of the vessel showing the slightest change, and it is perhaps sufficient to move the preparation one or two millimeters in order to come immediately upon another vessel that is already surrounded by a ring of corpuscles.

During this general emergence of colorless corpuscles at the outer periphery of the vessels, which always increases with the passage of time, and which, I shall state, I have observed on all the veins that run in the mesentery, from the smallest to the main trunks, in the interior of these vessels the original condition, previously developed and already described, maintains itself altogether unchanged. Before and afterward there lies in the inner marginal layer a simple unbroken deposit of white blood cells, and within these the red stream flows continuously. Finally it is not irrelevant to emphasize explicitly that not one red blood cell makes its appearance among the colorless corpuscles that emerge at the outer wall of the vessel.

This one fact will suffice to protect me against the incidental suspicion of so gross a delusion as that the corpuscles heaped externally around the vein have arrived there from a distance or that they have come out through a wound in the vessel itself. In reality, as I must assume, the account that I have given above, although it may depict the remarkable process incompletely, yet it must convince any unprejudiced person that the process consists of the extrusion of colorless blood corpuscles from the interior of the vein through the intact wall of the vessel . . .

Comment on Cohnheim

Cohnheim noticed that the inflammatory process shows wide variations and fluctuations of rate in different blood vessels and in different parts of the same blood vessel. He found that in the earliest stage the blood current lost its axial character, so that the peripheral zone, which normally contains plasma, became filled with colorless blood corpuscles. Hemispherical excrescences subsequently appeared at the outer borders of the vessels. He saw these outgrowths slowly change into piriform bodies, which ultimately became separated from the vessel and were then recognizable as emerged cells indistinguishable from the colorless corpuscles of the blood. This process of diapedesis he portrayed in fascinating detail.

In later parts of this treatise, not included in the foregoing excerpts, Cohnheim described similar observations made in young rabbits and kittens. Whereas he was regularly able to induce diapedesis, he usually could not produce a strongly purulent inflammation of the mesentery or very considerable exudates.

Acknowledging that his work contained gaps and that he had by no means answered every possible question, he had nevertheless succeeded in displaying and explaining the mechanism of inflammation with great accuracy. For this purpose he used varied techniques, at once simple and ingenious, which he deployed with skill, insight and limitless patience. He observed an immense number of details. These he combined into a coherent description which is one of the greatest contributions ever made in the entire history of pathology.

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Twenty-First Annual Scientific Session American College of Cardiology Chicago, Illinois, March 1–5, 1972

Method and Criteria of Selection of Abstracts for Presentation

A record 592 abstracts were received by the College for consideration for presentation at the 21st Annual Scientific Sessions. These abstracts were carefully reviewed by the Scientific Program Committee in the following manner. The 20 Committee members were divided equally into 2 similar teams comprising individuals representing adult cardiology, pediatric cardiology, cardiovascular surgery, pathology and basic science. Abstracts were sent at random to Team A or B. Thus, 10 members of either team graded each abstract objectively and independently from 1 to 10, with 10 being the highest, and the individual results were returned by each member to the Bethesda office of the College. In the case of an abstract from a reviewer's institution, the member abstained. The scores of each abstract were then averaged by the College staff. There was no significant difference between the overall average scores of the 2 teams, which were within 0.2 points of each other. All abstracts receiving 7.0 and above (125 abstracts) were automatically accepted for presentation. Those rated between 6.9 and 6.5 were discussed at a special meeting of all of the Committee members. It was possible to select a total of 168 abstracts for the final program.

DEAN T. MASON, MD, FACC
Scientific Program Chairman

Medical Versus Surgical Management of Cardiogenic Shock

SYED Z. ABBAS, MD*; K. R. SHANKAR, MD; G. COHEN, MD; Y. AKYREKLI, MD; W. J. KEON, MD, Ottawa, Ontario

Cardiogenic shock is the major cause of death in hospitalized patients with acute myocardial infarction. The results of intensive medical therapy and various forms of circulatory assist devices have been far from satisfactory. Between December 1970 and July 1971 7 patients—5 male, aged 43 to 66 years and 2 female, aged 47 and 57 years, respectively—underwent emergency aorto-coronary bypass grafts after intensive medical management was considered to be unsuccessful. All these patients had systolic blood pressure below 85 mm Hg and urine output less than 20 cc/hour, and the majority had cloudiness of sensorium. Two patients had complete heart block and 1, atrioventricular dissociation. Six patients underwent emergency selective coronary angiography without incident before surgery, and in 1 coronary angiography was performed 2 weeks before development of cardiogenic shock. Coronary angiograms showed occlusion of the right coronary artery (RCA) in 3; anterior descending artery (LAD) in 1; severe narrowing of LAD in 1 and high grade stenosis or occlusion of both LAD and RCA in 2.

Emergency bypass graft surgery was performed within 30 minutes after angiography, with 2 operative deaths. Five patients were eventually discharged from the hospital. One patient died of a cerebrovascular accident 2 months later. The other 4 are alive and well with 1 of them requiring digitalis and diuretic agents for control of heart failure. This limited experience is encouraging and has shown that emergency coronary angiography and aorto-coronary bypass surgery can be performed with gratifying results in this group of patients.

Clinical Significance of Ventricular Premature Beats in an Outpatient Population

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Ventricular premature beats (VPB's) may have important prognostic implications, particularly in patients with heart disease. This study was undertaken to test this hypothesis and to determine which other factors in patients with VPB's also influence mortality. All electrocardiograms (ECG's) performed on outpatients at the Lahey Clinic in 1967 were reviewed (total 12,751). One or more VPB's were present in 539 (42/1,000). All charts were reviewed, and the patients were grouped according to their most important medical diagnosis. Controls were selected, similar in all respects except for the absence of VPB's on the ECG. Followup was achieved in 99%, averaging 3½ years. The mortality rate was 17.1% in patients with VPB's and 10.7% in control subjects (1.6/1). This ratio is considerably less than that previously reported. In both VPB and control groups, the mortality rate in patients with heart disease was almost 6 times that of patients without heart disease. In the presence of underlying heart disease, and in association with certain ECG abnormalities, VPB's significantly influenced the mortality rate of VPB patients when compared with control patients. However, in the absence of heart disease and in the presence of an otherwise normal ECG, even frequent VPB's did not appear to affect survival. Particularly high mortality rates were noted in VPB patients with previous myocardial infarction (40%) and angina

* Abstracts are listed alphabetically, according to first author. Asterisk indicates the presentor.

pectoris (38.7%), and in both VPB and control patients with ECG evidence of left ventricular hypertrophy (32 and 56%, respectively). These data help to define the high-risk patient who may profit from prophylactic therapy.

Spontaneous Closure of Small Ventricular Defects. Probability Rates in the First 5 Years of Life

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Data on 55 infants with a clinical diagnosis of small ventricular septal defect made between 1967 and 1969 were reviewed. Recent physical examination data were obtained for 52. Spontaneous closure of the ventricular defect occurred in 30 patients (58%). The incidence of closure was considered separately for muscular (65%) and membranous defects (25%), as well as for those defects in which the anatomic position could not be determined clinically (58%). Age at closure, duration and intensity of the murmur, and the number of months of followup study in cases of non-closure were analyzed. As a practical index, the probabilities of closure by 5 years of age were calculated for patients theoretically presenting at birth, 1 year and 2 years of age. These were, respectively, 58, 48 and 35%.

Enhancement of Myocardial Function During Hypoxia by Increased Glucose Availability

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During myocardial ischemia anaerobic metabolism of glucose (G) provides the major source of energy to cardiac muscle. Therefore, augmentation of this metabolic pathway may improve energy supply and function of ischemic myocardium. Accordingly, isolated right ventricular cat papillary muscles were studied during normal oxygenation (95% oxygen, 5% carbon dioxide) and hypoxia (95% nitrogen, 5% CO_2). In 9 muscles supported by 100 mg/100 ml G, 2 successive periods of hypoxia were induced, each followed by 60 minutes of reoxygenation. Control peak isometric tension (T) during normal oxygenation, 4.7 g/mm^2, decreased to 1.2 and 0.8 during successive hypoxic periods. Time to peak T (TPT) also decreased significantly ($P < 0.05$). Two successive cycles of hypoxia-reoxygenation were studied in 7 additional muscles: 100 mg/100 ml G was utilized for the first and 1,000 mg/100 ml G for the second hypoxic period. Control T and TPT before hypoxia decreased to 18% (4.8 to 0.8 g/mm^2) and 64% (397 to 256 msec) with 100 mg/100 ml G. However, during support with 1,000 mg/100 ml G, hypoxia-induced reductions of T and TPT were attenuated ($P < 0.05$) to 27% (4.4 to 1.2 g/mm^2) and 86% (361–309 msec). In further studies on 6 additional muscles, augmentation of G from 100 mg/100 ml to 1,000 mg/100 ml during hypoxia significantly increased T (0.7 to 1.1 g/mm^2, $P < 0.01$) and TPT (240–290 msec, $P < 0.05$). During hypoxia in 6 muscles, insulin (I) (200 mU/ml) alone administered during hypoxia-100 mg/100 ml G increased T from 1.5 to 1.8 ($P < 0.05$). During hypoxia-1,000 mg/100 ml G, I increased T from 1.4 to 2.2 ($P < 0.01$). Increased glucose availability, achieved before or during hypoxia by G or I, enhances contractile function of hypoxic myocardium and thereby may an additional means of support for the ischei ing heart.

Potassium and Accelerated Purkinje Conduct

GARY J. ANDERSON, MD*; KALMAN GREENSPAN, P JOHN C. BAILEY, MD; CHARLES FISCH, MD, FACC, In Indiana

The purpose of this study was to delineate the physiologic mechanisms responsible for the relation between elevation of perfusing p (5.0–5.6 mEq/liter) and acceleration of co through the specialized conduction system of t One mechanism is that K^+ may suppress spo phase 4 diastolic depolarization. Impulses pro through areas showing spontaneous phase 4 de tion demonstrated prolonged conduction time K^+ superfusion, suppression of automaticity and impulse propagation was accelerated. mechanism for acceleration of conduction rel voltage time course of depolarization (phase 0 ductivity. Plotting dv/dt against phase zero m potential provided the characteristic "phase pla When this loop was interrupted by a 5 μsec ti generator, its acceleration could be calculated. maximal rising velocities ranged from 350 to 6 sec associated with action potential accelerati 18.7 to 21.0 megavolts/sec^2. Increasing the p Tyrode K^+ to 10.8 mEq/liter resulted in enhanc mal rising velocities (+10 to +15%) occurrin sue chamber K^+ of 5.2 to 5.6 mEq/liter. The la associated with enhanced phase zero accelerati to +30%), often to 25.0 megavolts/sec^2 and m enhanced action potential acceleration occurred ing potentials between −80 and −85 mv. It is s that at these resting potentials the difference i between resting potential and threshold potent duced, thereby accounting for enhanced accele phase zero. Thus, a faster rate of depolarizat act as a more effective and earlier stimulus t cent cells, thereby resulting in accelerated co Further elevation of bath K^+ resulted in a ma in resting potential, phase zero acceleration, rising velocities and depression of impulse tion.

Effects of Acetylcholine on His-Purkinje Autom and Conduction

JOHN C. BAILEY, MD*; KALMAN GREENSPAN, PH MARCELO V. ELIZARI, MD; GARY J. ANDERSON, MD GIDDINGS, MD; CHARLES FISCH, MD, FACC, In Indiana

This report describes the effects of acetylch small doses (4–8 μg/ml) on automaticity and tion within the canine proximal His-Purkinje The canine bundle of His and origins of bot branches were exposed in vitro while the pre was superfused continuously with oxygenated solution. Ultramicroelectrode impalement und visualization was then accomplished. Following recordings of action potentials demonstrati tively steep spontaneous phase 4 depolarization dition of acetylcholine caused significant slo the spontaneous rate, as well as a decrease in of diastolic depolarization. Concomitantly, tak

tential and rate of rise of phase 0 increased. Stimulating electrodes were then placed at various places on the proximal His-Purkinje system, and the preparation was electrically stimulated at a cycle length slightly less than its spontaneous rate. Impalement of 2 cells distal to the stimulating electrodes was then accomplished. After control conduction times were recorded, acetylcholine was superfused into the bath. This caused a marked decrease in stimulus-to-microelectrode and interelectrode conduction times associated with a decrease in the slope of phase 4 and an increase in take-off potential and rate of rise of phase 0. Our studies indicate that the canine proximal His-Purkinje system is responsive to a significant degree to the negative chronotropic effects of acetylcholine. This drug, by reducing the slope of phase 4 depolarization, hence increasing take-off potential, enhances conduction through this portion of the specialized conduction system.

An Improved Mitral Valve Prosthesis

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Approximately 5 years ago a Dacron® velour-covered Teflon®-disc mitral prosthesis was developed in an effort to reduce thromboembolic complications of mitral valve replacement. A 12 to 28 month followup study of 202 patients receiving these prostheses demonstrated an incidence of only 4.5% of such complications. This low incidence now has been confirmed by many investigators, including Morse and associates, who reported their experience with this prosthesis at the 1971 Annual Scientific Session of the American College of Cardiology. However, occasional edge wear of the original Teflon-disc necessitated change from extruded to compression-molded Teflon and thickening of the disc. Although significant wear of this modified disc has not been reported, a continuing search has been made for more durable materials. The most promising of these has been pyrolytic carbon, which has been used for both the disc and the struts of a similar prosthesis. Sacrifice of calves at intervals up to more than 9 months with scanning electron microscopic studies of the prostheses has demonstrated a disc and strut wear curve exceeding 100 years before significant wear.

Preliminary clinical investigations of the prosthesis have been associated with a low incidence of thromboembolic complications similar to that of the Teflon disc prosthesis, and these studies are continuing. Clinical use of this modified prosthesis now has been extended to several other centers. It appears to have significant advantages over currently available mitral prostheses and will be released generally in the early part of 1972.

The Cardiac Hemodynamic and Metabolic Responses to Coronary Arteriovenous Bypass Surgery

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Hemodynamic function and angiographic and electrocardiographic parameters were monitored in control subjects and in patients with proved coronary artery disease (CAD) before and after a pacing-induced stress. Samples were drawn from the coronary sinus and left ventricle for analysis of glucose, lactate, sodium, potassium, free fatty acid (FFA), triglyceride and oxygen. ^{14}Carbon-FFA uptake and metabolism were evaluated. In 10 CAD patients studied at rest preoperatively, mean heart rate (HR) was 79 beats/min ± 4 (SEM), left ventricular systolic pressure = 128 mm Hg ± 7, left ventricular end-diastolic pressure (LVEDP) = 13 mm Hg ± 2, time-tension index (TTI) = 1,004 ± 73, cardiac index (CI) = 3.3 liters/m^2 ± 0.2, total body O_2 consumption (QO_2) = 132 ml/min per m^2 ± 3, lactate extraction (LE) = 18% ± 4. With pacing, HR increased 75%, LVEDP +25%, TTI +64% and QO_2 +52%. Control subjects showed continuous lactate extraction during pacing. CAD patients showed immediate and persistent lactate production, but temporarily suppressed FFA extraction independent of arterial FFA concentration. This was accompanied by an enhancement of $^{14}CO_2$ production and fractional oxidation of ^{14}C-FFA (coronary sinus-arterial $^{14}CO_2$/arterial-coronary sinus ^{14}C-FFA). Throughout the study, both exhibited higher fractional extraction of ^{14}C- than of ^{12}C-FFA. Pacing eliminated this difference in CAD patients. Pacing induced an increase followed by a graded decline in FFA extraction in control subjects, the reverse of the CAD pattern.

In postoperative studies, following coronary arteriovenous bypass surgery, there were no significant hemodynamic or metabolic changes at rest. However, during pacing, LVEDP was 59% less, and QO_2 and CI decreased 21% and 28%, respectively. There was no significant lactate production. Studies revealed variations in ischemic carbohydrate and FFA metabolism during ischemia and suggest different regulatory controls. The surgical procedure enhanced aerobic metabolism, reduced anaerobic glycolysis and improved left ventricular function after a pacing-induced stress.

Scimitar Syndrome with Anatomic Variations

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The constellation of anomalies consisting of venous drainage of the right lung from a single pulmonary venous trunk entering the inferior vena cava, a degree of hypoplasia of the right lung and its pulmonary arterial supply and systemic arterial supply to one or more segments of the right lung from the thoracic and abdominal segments of the aorta constitute minimal criteria for the scimitar syndrome (MSS). The variations of this abnormality and the malformations of the cardiovascular system which may complicate it have received considerably less attention than the malformation itself.

We have extensively studied by radiographic, angiographic and hemodynamic techniques 3 patients whom we consider represent the spectrum of malformations which should be included to comprise the syndrome in toto. The abnormality may, from these studies, be classified into 3 aspects: (1) MSS without other associated abnormalities; (2) MSS with intracardiac abnormalities; and (3) MSS with systemic venous abnormalities. The patients included as representative examples of this classification have been found to have wide ranging variations in both the basic aspects of the syndrome and the complicating additional malformations. Analysis of the data discloses that patients with MSS may be

completely asymptomatic with minimal physiologic alteration and that the associated malformations may, by their effect, give rise to or increase the symptoms. This abnormality is considered to represent a primitive condition embryologically in which the only apparent counterpart in nature occurs in certain teleost fishes and the lungfish. This aspect of the defect will be discussed.

Treatment of Ventricular Arrhythmias Occurring During Acute Coronary Artery Occlusion in Conscious Dogs

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Since the majority of sudden deaths occurring after acute myocardial infarction (AMI) occur outside of hospitals and since these deaths are believed to be arrhythmic in origin, it has been suggested that the self-administration of atropine (A) or lidocaine (L) may effectively reduce mortality in AMI. To test the efficacy of these drugs in treating arrhythmias during the acute phase of AMI we studied 72 closed chest conscious dogs in which AMI was produced by inflating a balloon cuff previously implanted around the left anterior descending artery. Ventricular arrhythmias developed in 52 dogs either during occlusion or within 2 minutes of release of occlusion. Arrhythmias were treated by (1) atrial pacing at 110 to 120/min, (2) A (to increase heart rate to a maximum of 125 beats/min), (3) L (2–3 mg/kg), and (4) A+L. Of the 18 dogs in which ventricular fibrillation (VF) developed, all had ectopic ventricular beats that followed a preceding beat (R–premature ventricular contraction [PVC] interval) by ≤ 0.43 sec. In treated dogs, arrhythmias were suppressed as shown in Table I. We conclude that although

TABLE I

Suppression of Arrhythmias

R–PVC interval	Pacing	A	L	A+L
>0.43 sec	10/12	11/14	3/8	2/3
≤0.43 sec	3/15	2/17	0/6	1/7

these interventions successfully suppress most slow arrhythmias, they appear relatively ineffective in suppressing those faster arrhythmias that lead to precipitation of VF.

Assessment of Aortocoronary Saphenous Vein Bypass Function Utilizing Selective Indicator-Dilution Curves

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Evaluation of aortocoronary saphenous graft function was performed with the selective indocyanine green indicator-dilution method in 20 postoperative patients. In addition, all subjects underwent complete left and right heart catheterization, selective coronary artery and bypass graft cineangiography. Selective indicator injections were made into the aortic root, diseased coronary artery and saphenous bypass graft with constant sampling at the main pulmonary artery. There were negligible electrocardiographic changes associated with indicator injection.

The graft dilution curves obtained from such testing were analyzed with respect to corrected appearance time (AT), build-up time (BT), clearance time (CT), mean transit time (MTT), peak amplitude (PA) and contour. When compared with aortic root indicator injection, characteristic findings were: (1) patent graft with good flow—early AT and BT, short CT and MTT with a high PA; (2) partially occluded graft with moderate flow—later AT and BT, longer CT and MTT, and lower PA with notching, slurring and a "double humped" ascending limb; (3) totally occluded graft with no flow—no difference from curves obtained with aortic root indicator injection. These alterations correlated well with evaluation of graft patency using selective saphenous graft angiography. Dye-dilution curves obtained from injection of the bypassed coronary arteries permitted assessment of the disease in these vessels and the relative contribution of these vessels to myocardial blood flow. The results indicate that this technique is safe and useful for the evaluation of bypass graft function.

Wolff-Parkinson-White in the Neonate; 9 Cases Including 2 with Intrauterine Defects

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Wolff-Parkinson-White syndrome (WPW) was diagnosed in 9 neonates aged 5 hours to 26 days. Of 4 without associated congenital heart disease (CHD), 2 had intrauterine tachycardia and were born with cardiac failure; in 2, paroxysmal atrial tachycardia (PAT) developed at age 2 and 11 days, respectively. All 4 had type A WPW. On followup study, WPW disappeared in 3 and persisted in 1. Five patients had WPW with associated CHD. Cardiac diagnoses were confirmed in all and included 2 cases of complete transposition of the arteries and 1 each of corrected transposition, patent ductus arteriosus with multiple noncardiac anomalies and aortic valve atresia. WPW was of type B in 4 of the 5 neonates and has persisted on followup study in the 3 survivors.

Review of 35 cases of WPW in the neonate including 26 from the literature and these 9 cases showed that WPW in the neonate is frequently complicated by PAT which leads to congestive failure. Of 25 neonates without CHD the majority were male (78%); the WPW was usually type A (85%); all but 2 had documented PAT; and on followup study WPW had disappeared in 43%. Of the 10 cases of WPW with associated CHD all were male; WPW was of type B in 78%; only (30%) had PAT; and WPW persisted on followup study in the 5 survivors.

In summary, WPW in the neonate without associated CHD is usually of type A and often transient. Type B WPW should suggest associated CHD. The variety of lesions reported indicates that cyanosis associated with WPW does not always mean Ebstein's malformation as has been previously suggested.

Congenital Polyvalvular Disease

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Diffuse involvement of all the valves, or what we are calling *congenital polyvalvular disease*, was observed in

25 of the 3,400 congenitally abnormal hearts seen in this center in the last 14 years. The common feature in this entity was marked thickening and deformity of the valves, with redundant tissue and marked nodularity. This involved mostly the tricuspid and pulmonic valves, less the mitral and least the aortic valve. The pulmonic and aortic valves were in many instances bicuspid or unicuspid. The changes noted were too severe and bizarre to be attributed to hemodynamic stress. Microscopic examination of the valves revealed marked proliferation of spongiosa. This disease could be classified into 4 groups: (1) with shunt, 14 cases; (2) with obstruction, 2 cases; (3) with obstruction and shunt, 8 cases; and (4) without obstruction or shunt, 1 case.

Congenital polyvalvular disease was associated with multiple congenital abnormalities. In 4 cases trisomy 18 was proved. Clinically, trisomy 18 was suspected in 12 additional cases because of the low-set ears, peculiar looking facies and other manifestations typical of trisomy 18, but chromosomal studies were not performed. In 1 case, the mother had had rubella in the first trimester of pregnancy; in another, the mother was diabetic, and in still another the mother had rheumatic heart disease. Three cases were associated with glycogen storage disease, and in 1 both glycogen storage disease and proved trisomy 18 were found.

We believe that polyvalvular disease constitutes a distinct entity related to trisomy 18.

Learned Control of Ventricular Rate in Patients with Atrial Fibrillation

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Normal men can be trained to slow, speed and cyclically slow and speed heart rate (HR) when provided electronic feedback about their HR on a beat to beat basis. Feedback consists of a light display which turns on when the subject correctly modifies HR and turns off when he does not. HR control in normal sinus rhythm occurs by modification of the sinus pacemaker. HR in complete heart block cannot be modified voluntarily. The purpose of this study was to determine whether learned HR control can be mediated at the atrioventricular (A–V) node.

Six patients with atrial fibrillation (AF) receiving maintenance doses of digitalis were trained to slow and speed ventricular rate (VR). Two subjects consistently slowed VR; 2 subjects consistently speeded VR; and the other 2 subjects reliably slowed and speeded VR. All subjects were able to cyclically control VR during sequential slowing and speeding phases of training sessions. Analyses of R–R interval histograms revealed that all subjects significantly changed the statistical frequency distribution of their R–R intervals. During VR slowing 1 subject generated a junctional escape rhythm. Another subject produced frequent premature ventricular contractions during VR speeding under effective beta adrenergic blockade with propranolol.

This control of VR in AF is neurally mediated at the A–V node. Studies with autonomic drugs indicate that central nervous system control of VR in AF usually occurs through activation of efferent cholinergic pathways.

Functional Development of the Coronary Collateral Circulation During Acute Myocardial Infarction in the Conscious Dog

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We studied changes in the coronary collateral circulation during acute myocardial infarction in 14 conscious dogs by (1) determining simultaneous changes in peripheral coronary pressure (PCP) and retrograde flow (RF) after abrupt coronary artery occlusion; (2) correlating these functional indexes with quantitative anatomic indexes of coronary collateral development (Menick et al. Amer Heart J 82: 503–510, 1971); and (3) observing changes in these indexes after repeated occlusions of a coronary artery. These dogs were subjected to left circumflex coronary artery (LCCA) occlusions for 2 hours to 8 days, and had pressure tubes implanted in the aorta and LCCA, the latter tube placed distal to an occlusive cuff for PCP and RF measurements. The animals were then killed, their hearts injected with a modified Schlesinger's gelatin mass and AI determined.

During 2 to 24 hour LCCA occlusions (11 dogs) mean PCP increased to levels of 50 to 80% of prevailing aortic pressure. During repeated 2 to 24 hour occlusions (2 dogs) in the same dog the rate of PCP rise increased. RF was unchanged during 2 to 24 hour occlusions. Anatomic indexes of these dogs were in the same range observed in control dogs that did not undergo occlusions. When LCCA occlusion was maintained for more than 4 days (3 dogs), mean PCP increased during the first 24 hours and then remained stable. RF did not change until 4 days of occlusion and then increased. Anatomic indexes of dogs undergoing occlusion for more than 4 days were significantly greater ($P < 0.001$) than those of dogs undergoing occlusion for 2 to 24 hours.

Our study shows (1) that the early PCP rise after occlusion is *not* associated with an increase in RF; (2) that RF is a better index of collateral function; and (3) that RF correlates well with the anatomic development of the collateral bed.

The Value of Continuous Monitoring of Cardiac Muscle Performance

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The left ventricular contractility as expressed by isometric maximal velocity of contractile elements shortening (Vmax) was calculated at frequent intervals, before and after cardiac operation in 15 patients, and in 1 patient during cardiac catheterization. The calculations were based on readings of the left ventricular pressure (P) and its first derivative (dp/dt) obtained from an indwelling high fidelity pressure tip catheter transducer. Vmax was extrapolated from the contractile element velocity (VCE) curve by application of

a 2-component muscle model and using the formula $VCE = \frac{dp/dt}{P}$, (K = 28). Retrospective analysis of data, obtained for an average of 3 days postoperatively, showed that among 7 patients undergoing aortocoronary bypass graft with preoperative mean Vmax of 1.07 ± 0.13 circumferences/sec, there was no statistically significant change in myocardial contractility for up to 72 hours after the operation. In 7 patients having aortic valve replacement, immediately after surgery the Vmax decreased from control value of 0.88 ± 0.09 to 0.63 ± 0.5 ($P < 0.05$), but returned to control 6 hours after the operation. In 2 patients who experienced acute myocardial ischemia and infarction after coronary surgery and during cardiac catheterization, there was an associated decrease in Vmax relative to the extent of cardiac muscle loss. In 2 other patients, who eventually died because of progressive heart pump failure following cardiac value surgery, the Vmax gradually declined and remained at a low value in spite of therapy with digitalis or isoproterenol infusion. These studies indicate that in selected patients it is possible to obtain serial valid data on myocardial contractility which may serve as diagnostic and predictive indexes.

Progression of Proximal Coronary Arterial Lesions to Total Occlusion After Vein Graft Surgery and Its Effects

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Four patients with severe angina had 6 vein bypass grafts placed for 1 complete and 5 severe but incomplete (90%) proximal coronary arterial narrowings. Coronary angiography 6 months after surgery showed no forward passage of opaque medium past the 5 previously incomplete stenotic points. Injection of the grafts demonstrated that they were patent and providing good distal filling. In 2 patients, after graft injection, there was retrograde opacification up to and even beyond the points at which there was no antegrade passage of dye, thereby indicating that there was no anatomic occlusion but rather hindrance to forward flow by restoration of pressure in the post-stenotic segment. Both these patients experienced significant and sustained relief from their angina. In the other 2 patients no such retrograde opacification was demonstrable, thus suggesting that anatomic complete occlusion had developed. These 2 patients experienced recurrence of angina after some initial improvement, and 1 sustained an anterolateral myocardial infarction despite apparently good perfusion of the distal anterior descending artery by the graft.

These observations confirm previous reports of rapid progression of proximal lesions after distal coronary vein graft surgery and raise the possibility that the bypass may play a causative role. In 1 patient the functioning venous graft did not prevent the occurrence of a myocardial infarction in the territory of the bypassed artery, a premise upon which recommendations are based for prophylactic coronary arterial surgery in patients with few or no symptoms.

Rapid On-Line Computer Determination of Left Ventricular Contractility During Pacemaker Tachycardia in Man

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Currently, the determination of left ventricular contractility (LVC) is a laborious process. Over 100 studies in 12 patients demonstrated LVC computation by determining Vmax continuously in real-time by utilizing a novel computer graphics program. Left ventricular pressure (LVP) and its first temporal derivative (dp/dt) were recorded via transducer tip catheters (P866).

A process control computer (EMR 6130) continuously calculated contractile element velocity (CEV) from these digitized signals via the equation relationship CEV = (dp/dt)/32·(LVP). As LVP and dp/dt data points were obtained, the relation of CEV vs. LVP for isovolumetric contraction was plotted on a graphics terminal. Maximal dp/dt, time to peak tension, CEV at 5 mm Hg LVP, CEV maximum, and CEV extrapolated to 0 LVP (Vmax) were displayed on the CEV vs. LVP plot. Each complete contractility computation and plot required 3 seconds in comparison to 30 minutes by usual methods. Data on cardiac output (CO), ventricular volume and ejection fraction (EF) were simultaneously obtained at rest and during right atrial pacing (rates from 100 to 180/min). Six patients had diminished LVC (D) with EF $\leq$ 0.40; 6 patients of similar age and weight had normal contractility (N) EF $\geq$ 0.55. At the example heart rate of 120/min no significant difference between N and D for CO, LVP or maximal dp/dt was found. CEV at 50 mm Hg LVP for N (mean 0.84, SE ±0.10) was greater than for D (0.59 ± 0.04) ($P < 0.05$); this difference increased with pacing. Maximal CEV was not significantly different for the 2 groups at rest but became so with tachycardia. CEV extrapolated to 0 LVP (Vmax) was significantly larger for N (1.18 ± 0.14) than for D (0.79 ± 0.09) ($P < 0.05$). With pacemaker tachycardia N (1.51 ± 0.13) increased to larger extent than D (0.96 ± 0.06) ($P < 0.005$).

Thus, rapid computer determination of CEV yields measures of contractility more sensitive to myocardial change than CO, LVP or dp/dt max. Vmax with tachycardia provided the most sensitive contractility measure for our groups.

Myocardial Infarct Size in Man Assessed by Serial Serum Creatine Phosphokinase Changes

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To ascertain whether infarct size is a critical determinant of prognosis in man, it was assessed quantitatively in 25 patients with acute myocardial infarction. We have recently developed a method to measure infarct size in the conscious dog by analysis of serum creatine phosphokinase (CPK) changes with respect to CPK distribution space, disappearance rate, myocardial degradation, and release into the circulation and have validated the method by measurement of myocar-

dial CPK depletion in the same animals. In the present study, CPK activity (determined spectrophotometrically) and isoenzyme profiles (assayed electrophoretically) were measured in patient serum samples obtained every 2 hours. Infarct size was determined by mathematical analysis of serial CPK changes utilizing the method previously developed in the conscious dog model. CPK isoenzyme profiles demonstrated prominent anodal bands, absent from normal serum, indicating that enzyme elevations reflected CPK released from heart rather than skeletal muscle. In 15 survivors in class I and II (New York Heart Association), infarct size was 24 ± 4.1 g (mean ± SE). It was significantly larger, 68 ± 5.2 g, in 10 patients who died with congestive heart failure or survived in class III or IV ($P < 0.01$). All 5 patients with infarcts associated with single peaks of myocardial CPK release survived in class I and II, whereas 8 of 20 patients with serial CPK results demonstrating repeated bouts of necrosis died. Determination of cumulative infarct size differentiated patients with extension of infarction from those with electrocardiographic changes and clinical sequelae from complications such as pericarditis. Thus, infarct size can be determined quantitatively in patients with acute myocardial infarction, providing a useful diagnostic and prognostic index based on the extent of myocardial damage.

Healed Valvular Infective Endocarditis

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Of 29 necropsy patients with healed valvular infective endocarditis (IE), active IE had occurred on previously anatomically abnormal valves in 24 (83%), 9 of whom had congenitally bicuspid aortic valves. Vegetations had involved the aortic valve alone in 17 patients, the mitral valve alone in 4 and both valves in 8. The causative organisms were *Streptococcus sp.* in 14 patients and *Staphylococcus sp.* in 5. All 29 patients had valvular dysfunction during and after active IE; 27 had congestive heart failure (CHF). Active IE caused or contributed to the valvular dysfunction in at least 22 patients. In no patient did CHF develop de novo after cure of active IE but, in each, progressive intractable CHF occurred leading to death (12 patients), or to operation with subsequent death (17 patients). Focal myocardial fibrosis occurred in 24 patients (92%) and focal necrosis in 9 (34%). Microscopic-sized myocardial lesions were frequent but were not major factors in causing CHF in patients with healed IE. Patients surviving active IE tended to have the infection on previously abnormal valves, and the organisms were usually relatively nonvirulent. Of 57 other patients who died during active IE, the infection was usually (61%) on previously normal valves, and the organisms were usually highly virulent.

A Study of the Ventricular Activation Process in Preexcitation Syndrome Using His Bundle and 1 mm Apart Bipolar Electrograms

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Bipolar catheter leads with interelectrode distances of 1 mm were used to determine arrival of excitation at the His bundle area, right ventricular apex (RVA) and right ventricular outflow tract (RVOT). Four patients with Wolff-Parkinson-White (WPW) syndrome were studied (3 with type A and 1 with type B). The hallmark of exclusive "E" or predominant "P" accessory bundle conduction (ABC) was the inscription of a forward H deflection after the onset of ventricular (V) depolarization. In the patient with WPW type B the V–RVA and RVA–RVOT intervals measured 20 and 10 msec, respectively, in beats with pure His bundle conduction, and 0 and 60 msec, respectively, during ABC. Hence, the RVA was activated by the impulse descending through the right branch in the former instance, and from the relatively close preexcited area during ABC. The 3 patients with WPW type A had QRS complexes resulting from (1) "E" His bundle conduction with normal intraventricular conduction, (2) "E" His bundle conduction with right bundle branch block, and (3) "E" or "P" ABC. In (1) there were normal H–V, V–RVA and H–RVA intervals. During (2) the V–RVA interval was prolonged, indicating that the RVA was activated by the impulse descending through the left bundle system (after crossing the septum). On the other hand, "fusion" beats with "P" ABC had normal H–RVA intervals, suggesting that the RVA was excited through the right branch. Finally, during "E" ABC significant prolongation of the V–RVA indicated that the RVA was not depolarized through the right branch, or left bundle systems, but from the preexcited area. It is concluded that His bundle and local electrograms have enhanced knowledge of intraventricular conduction in the preexcitation syndrome.

Influence of Aortocoronary Artery Bypass on Left Ventricular Asynergy

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Segmental systolic contraction patterns (anterior wall motion [AWM], apical motion [APM] and inferior wall motion [IWM]) were determined from single plane right anterior oblique cineangiograms before and after aortocoronary artery bypass surgery in 19 patients with coronary disease, and were compared to those of 6 normal control subjects. In patients with normal preoperative segmental contraction patterns, no significant change was observed postoperatively. In 8 patients AWM (4–30%, mean 19%) was less than normal (range 31–63%, mean 52%). In 5 of these, AWM returned to normal range after successful aortic-left anterior descending (LAD) coronary artery bypass. In 1 patient with old anterior infarction, 1 with unsuccessful LAD bypass and 1 with RCA bypass only, AWM remained unchanged postoperatively. In 12 patients (10 with LAD and 2 with left circumflex disease), APM (range 3–30%, mean 14%) was less than normal (26–40%, mean 33%) preoperatively. Following appropriate bypass, APM returned to the normal range in 9 of 12 patients. In 2 with unsuccessful LAD bypass, APM was reduced and in 1 with RCA bypass was unchanged. In 7 patients, IWM (9–25%, mean 14%) was less than normal (27–54%, mean 41%) preoperatively. In 3, after successful coronary artery bypass, IWM returned to the normal range. Of the other 4 patients, in 3 with previous inferior infarcts, IWM remained unchanged. In 1 without previous infarct and with successful by-

pass, no change occurred. These findings indicate that in patients with left ventricular asynergy not due to infarct, appropriate aortocoronary bypass can improve segmental contraction patterns.

Comparison of the Beta Adrenergic Blocking Properties and Negative Inotropic Effects of Oxprenolol and Propranolol in Patients

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The effectiveness of beta receptor antagonists as potent antiarrhythmic agents has prompted considerable effort in developing newer compounds with attenuated negative inotropic properties so that their usefulness can be extended to patients with reduced myocardial reserve. Thus, the inotropic and beta blocking properties of oxprenolol (Ox) were evaluated in 8 patients at diagnostic left heart catheterization and compared with propranolol (Prop) in 6 additional subjects. Fifteen minutes after intravenous administration of Ox (5 mg), heart rate (HR) slowed significantly from 74.7 to 65 beats/min ($P < 0.01$). However, left ventricular end-diastolic pressure (LVEDP) (11.3–11.1 mm Hg) and stroke volume index (SI) (41–39.4 ml/m^2) were unchanged (NS). In contrast, Prop (5 mg intravenously) significantly reduced HR (78.2–65.2, $P < 0.01$) and increased LVEDP (9.7–14.8, $P < 0.01$), without changing SI (38.4–38.8, NS), thus suggesting a reduction in myocardial contractility. The first derivative (dp/dt) of high fidelity left ventricular pressure (LVP) at 50 mm Hg (dp/dt [50]) was unchanged after Ox (1,277–1,185 mm Hg/sec) but was reduced by Prop (1,545–1,330, $P < 0.02$). Contractile element velocity (VCE = dp/dt/32·developed LVP) plotted against instantaneous developed LVP and extrapolated to 0 LVP (Vmax) was unchanged after Ox (1.02–1.02 muscle lengths/sec, NS) but was significantly reduced after Prop (1.38–1.28, $P < 0.02$). At this dose, both drugs are equipotent beta blockers; Ox attenuated the isoproterenol-induced (1 μg intravenously) increase in HR 78%, dp/dt [50] 93% and Vmax 93%, similar to Prop (78, 98, and 100%, respectively). Therefore, in equivalent mg and beta blocking doses, Ox appears to possess considerably less negative inotropic effect than Prop.

The Clinical Triad of Traumatic Ventricular Septal Defect, Occlusion of Left Anterior Descending Coronary Artery and Ventricular Aneurysm

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Although it is appreciated that acquired ventricular septal defect (VSD) can result from acute myocardial infarction, particularly with occlusion of the left anterior descending coronary artery (LAD), it is not well recognized that VSD can occur with both penetrating and blunt chest trauma. VSD may develop acutely or several days after the trauma. Five consecutive patients with traumatic VSD (1 blunt, 4 penetrating) were catheterized including left ventricular and coronary angiography. The average pulmonic to systemic flow ratio was 2:1, with shunting clearly documented at the ventricular level. Three patients also had a left ventricular aneurysm, and 2 had localized occlusion of the LAD. It appears that closed or penetrating injury to the anterior precordium which produces a VSD, may interrupt the LAD. The ventricular aneurysm results from the LAD occlusion or from the associated myocardial trauma itself. Thus when traumatic VSD occurs because of blunt or penetrating injury, the remaining components of the clinical triad (LAD occlusion and ventricular aneurysm) should be anticipated, diligently sought, and considered in the management of this defect.

Ultrasound Determination of Mean Fiber-Shortening Rate in Man

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Recently it has been shown that cineangiocardiographic measurement of the mean rate of circumferential fiber shortening (MRFS) at the minor left ventricular equator is a reliable method for evaluating the mechanics of cardiac performance. However, an accurate noninvasive method for assessing left ventricular myocardial mechanics would be desirable. Accordingly, in 16 patients the MRFS in the plane perpendicular to the interventricular septum and left ventricular posterior wall was measured by reflected ultrasound, and compared with the MRFS derived from a cineangiocardiogram performed within 24 hours of the ultrasound determination. The MRFS by ultrasound averaged 1.0 circumferences/sec (range 0.54 to 1.44) and correlated well with the MRFS measured by angiography ($r = 0.90$, $P < 0.01$).

The ultrasound technique detected abnormal myocardial function in 93% of patients. One additional patient with marked anterior wall dyskinesis and a reduced MRFS by angiography had a normal MRFS by ultrasound. The ejection fraction (EF) derived from ultrasound measurements averaged 0.55 (range 0.33 to 0.77) and correlated significantly with the EF calculated by cineangiography ($r = 0.85$, $P < 0.01$). By ultrasound, EF correlated well with MRFS ($r = 0.96$, $P < 0.01$), and by cineangiography the correlation was also significant ($r = 0.90$, $P < 0.01$). The average maximal velocity of posterior wall motion was 4.2 cm/sec (range 1.9 to 6.4) and did not consistently distinguish normal from impaired cardiac function. It is concluded that in the absence of marked anterior wall dyskinesis, ultrasound measurement of MRFS is a reliable noninvasive technique for the evaluation of left ventricular performance.

Production of a Myocardial Depressant Factor in Shock Following Acute Myocardial Infarction: Preliminary Evaluation of Treatment With Methylprednisolone

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In 13 of 15 patients with cardiogenic shock (CS) after acute myocardial infarction (AMI), plasma concentrations of a myocardial depressant factor (MDF, normal 15–25 units) and cathepsin D or B-glucuronidase were

elevated in all cases. Treatment with methylprednisolone (MP), 30 mg/kg per 24 hours, was related to mean arterial blood pressure (MABP), urine flow, plasma MDF and survival before treatment, at 4 hours and during convalescence. Five patients treated conventionally died; 3 showed elevated plasma MDF at 40, 54 and 58 units, respectively. In 10 before MP treatment, the mean plasma MDF was 45 ± 3 SEM units which fell to 31 ± 4 ($P < 0.01$) 4 hours after initiation of MP treatment. In 3 survivors, MDF was normal 2 weeks or more after recovery from CS. Thirteen of 15 patients had low MABP (70 mm Hg or less) at the initial sample of MDF. The MABP in the 10 treated with MP was 52 ± 6 SEM mm Hg before treatment, and 4 hours after MP was 66 ± 8 (no significant difference). In the 5 (50%) who survived with MP treatment, the MAPB was 57 ± 7 initially and 80 ± 6 mm Hg ($P < 0.05$) 4 hours after initiation of MP. Mean urine flow was 7 ± 3 SEM ml/hour before treatment for all 15 patients. In the 10 treated with MP, mean urine flow rose to 70 ± 24 ml/hour 4 hours after onset of treatment ($P < 0.02$).

The fall in plasma MDF and increase in urine flow suggests that administration of MP leads to diminished production of MDF and possibly to increased excretion of MDF via the kidneys. The results suggest that MDF and lysosomal hydrolases may be important in the pathogenesis of CS. Survival was 50% with treatment with MP; CS mortality with conventional treatment in this unit is 83%. Since MP appears to reduce plasma MDF during amelioration of CS, glucocorticoids may have positive value in achieving survival in certain cases of CS due to AMI.

The Effect of Glucagon on the Ventricular Response in Atrial Fibrillation—A Possible Hazard

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We studied the comparative effects of glucagon, ouabain, norepinephrine and combined atropine and propanolol on left ventricular (LV) function, mean cycle length and mean ventricular rate in awake conscious dogs during experimental atrial fibrillation (AF) produced by bipolar left atrial stimulation at 20 Hz, 5 v, and 3 msec duration. Nine dogs were studied 9 to 60 days after surgery. Simultaneous recordings were made of dLnP/dt, dp/dt, LV pressure, left atrial pressure, LV internal diameter, the left atrial electrogram and LV electrogram. An analysis was then made of 400 or more consecutive cycles during the control period and after each intervention. The observed changes in average ventricular rate and average total cycle length are listed in Table I for each intervention.

TABLE I

Observed Changes

Intervention	Average Total Cycle Length (msec)	Average Ventricular Rate/Min
Control	602	97
Ouabain (20 mg/kg)	646	93
Norepinephrine (1.5 mg/kg per min)	522	115
Atropine (2 mg) + propranolol (12 mg)	316	190
Glucagon (50 mg/kg)	176	340

During periods of AF, glucagon caused the ventricular rhythm to become regular, and the ventricular rate rose to 340 beats/min. Apparently this effect was due to the ability of glucagon to increase the rate of atrioventricular conduction and decrease the duration of the "concealment zone" during fibrillation. Glucagon administration may be hazardous in patients with AF. The hemodynamic and electrophysiological implications of these findings will be discussed.

Adenyl Cyclase Activity in Experimental Myocardial Hypertrophy

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Adenyl cyclase activity (ACA) was measured in experimental myocardial hypertrophy produced by supravalvar aortic narrowing in mature female rats. The ascending aorta was constricted to approximately 30% of original size, producing peak systolic gradients of 70 to 80 mm Hg between the left ventricle (LV) and aorta. Studies at 1 and 24 hours failed to reveal increased LVED pressure or other signs of congestive heart failure. Left ventricular mass increased by 10% in 24 hours as compared to sham operated controls. Ribonucleic acid (RNA) polymerase activity increased by 10% at 12 hours, and by 30 to 40% at 24 hours. No increase in RNA synthesis was detected at 1 hour. ACA in the LV began to decrease by 1 hour and became significantly less than that of sham controls at 24 hours (227 ± 14 vs. 257 ± 21 pmoles cyclic adenosine monophosphate [AMP] protein per 10 minutes of incubation [$P < 0.05$], respectively). ACA of LV tended to be lower than that of right ventricle (RV) in the sham operated animals ($P > 0.10$). This difference was significant in the constricted animals at 1 hour (RV 225 ± 14, LV 195 ± 19, $P < 0.05$) and 24 hours (RV 284 ± 29, LV 227 ± 14, $P < 0.05$). Decrease in ACA has been reported in experimental congestive heart failure. However, our animals did not manifest definite cardiac failure. Cyclic AMP, the end product of adenyl cyclase, has also been implicated in the stimulation of RNA polymerase activity. In our studies RNA polymerase stimulation appeared to occur while adenyl cyclase activity was depressed. These findings suggest that RNA synthesis during experimental hypertrophy is not necessarily dependent on adenyl cyclase activity.

Objective Index of Hemodynamic Status for Quantitation of Severity and Prognosis of Shock Complicating Myocardial Infarction

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The relative importance of individual and groups of hemodynamic indexes was assessed in 30 patients with acute myocardial infarction and shock. This study updates a preliminary report presented at this meeting in 1967. Patients were observed over an average period of 25 hours. Hemodynamic measurements obtained from each patient included values for intraarterial systolic, diastolic (DP) and mean pressures, central venous

pressure, heart rate, cardiac index (CI) and stroke index (SI), vascular resistance, mean circulation and appearance times of dye and central blood volume (CBV). Six patients survived, and 24 died. Individual measurements reflecting SI or CI were more reliable than measurements of arterial pressure as indicators of survival. Changes in arterial pressure were of limited value in reflecting changes in flow, with correlations ranging from −0.28 to +0.04.

Sets of observations from survivors and from patients who died were compared by use of discriminant function (DF) analysis. With the use of 3 hemodynamic variables, SI, DP and CBV, in each observation set, the outcome was predicted with an estimated accuracy of 91%. However, only 2 variables, SI and DP, contributed significantly to the DF, giving a reliability of 88%. The DF based on these variables was DF = 0.23104 SI + 0.13447 DP. DF analysis was then used to assess the reliability of subsets of variables. Among these, subsets that included the value for SI or CI showed greater ability to predict outcome than subsets in which values of other variables were substituted. A theoretical estimate of probability of survival (PS) was derived for any value of the DF. The DF, or its equivalent, PS, serves as an indicator of the severity of shock. We anticipate practical application of these prognostic measurements for selection of patients who, after onset of pump failure, are to be candidates for assisted circulation or emergency surgical treatment.

Plasma Volume in Shock Associated with Myocardial Infarction

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As an extension of a study previously reported at these meetings, changes in plasma volume (PV) were assessed in 18 patients in shock associated with acute myocardial infarction (AMI). PV was measured using ^{121}iodinated human serum albumin with isotope activity determined at intervals of 15, 25, 35 and 45 minutes after injection. Measurements of PV were obtained in 5 survivors and 13 patients who died on admission and after an average interval of 26 hours. Treatment included administration of a vasopressor agent (metaraminol) in all but 1 patient. The initial plasma index (PI) was normal in both groups, averaging 42.9 ± 3.4 ml/kg in survivors and 44.7 ± 3.9 ml/kg in patients who died. However, the initial right atrial pressure in survivors, which averaged 6.0 ± 2.1 mm Hg, was significantly less than in patients who died (mean 11.3 ± 1.3 mm Hg, $P < 0.05$).

The volumes of crystalloid fluids infused into survivors and patients who died were approximately the same and averaged 87 ml/hour. The PI increased significantly to 57.9 ± 5.3 mm Hg in survivors, and central venous pressure (CVP) remained within normal limits (7.8 mm Hg). However, the PI was essentially unchanged in patients who died (mean 44.5 ± 3.9 mm Hg). Although the CVP decreased slightly, it remained in an elevated range (9.6 ± 1.0 mm Hg). The PI in survivors was significantly higher at time of discharge from our unit in comparison to PI recorded before death ($P < 0.05$). Although a further increase in CVP after fluid challenge was not observed in patients who died, autopsy findings revealed increased lung weight (mean 1,452 ± 148 g). Marked edema was present in 7 of 9 patients.

Augmentation of PV in patients with shock following AMI is associated with increased survival. However, the prognosis is poor when the PV is not expanded after fluid challenge.

Hemodynamic Changes One Year After Acute Myocardial Infarction

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Hemodynamic studies were performed in 22 patients at the time of acute myocardial infarction (AMI) and an average of 13 months later, to determine the relation between clinical course and change in hemodynamics. Despite complete clinical recovery in most cases, there was a significant decrease in cardiac output (CO) (mean ± SD) from 6.2 ± 1.7 to 4.9 ± 1.5 liters/min. There was also a significant decrease in oxygen consumption (O_2C) from 298 ± 92 to 235 ± 85 ml/min. Arteriovenous oxygen difference (AVD) and the ratio CO/O_2C were normal in both studies and did not change significantly. There were significant decreases in right atrial pressure (9.6 ± 3.8 to 6.6 ± 3.0 mm Hg) and in heart rate (80 ± 16 to 65 ± 12 beats/min). Arterial pO_2 increased from 63 ± 15 to 79 ± 12 mm Hg. Clinical course in individual patients correlated best with changes in AVD. Patients who recovered from congestive heart failure had a decrease in AVD; those with persistent heart failure showed an increase in AVD.

This study suggests that the relatively high values of CO and O_2C measured at the time of AMI were a result of stress, and that the lower, more normal values obtained 13 months later represented a more basal state rather than a decrease in cardiac function. CO determinations obtained at the time of AMI should be interpreted in conjunction with O_2C and AVD to evaluate the role of stress.

The Clinical Course of Cardiomyopathy Associated with Alcoholism

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Sixty-four patients (57 male and 7 female) who had cardiomyopathy associated with alcoholism were followed up for an average of 46 months (range 4 months to 10 years). They were not treated with prolonged bed rest. The clinical status of 12 patients was improved, remained stable in 20 and deteriorated in 6. Twenty-six patients died. Of 42 patients who continued to drink heavily, the status has improved in 2 (5%), is unchanged in 12 (28%), and has deteriorated in 4 (10%); 24 patients (57%) are dead. The remaining 22 patients either stopped drinking or seriously curtailed their drinking. Of these 22 patients, the status has improved in 10 (44%); is unchanged in 8 (36%), and has deteriorated in 2 (9%); 2 patients (9%) have died. Ten of the 64 patients have had a return of heart size to normal. In these patients the average duration of symptoms before therapy was 2.2 months. The average duration of symptoms in the remaining 54 patients

was 13.8 months. The clinical course of these patients was comparable with that of patients treated by other workers with prolonged bed rest. A short duration of symptoms before therapy and abstention from alcohol were the 2 most important factors that determined a more favorable course in patients with alcoholic cardiomyopathy.

Echocardiographic Features of Torn Chordae Tendineae

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This study describes the echocardiographic findings in 6 patients with surgically proved torn chordae tendineae. In 4 patients the torn chordae involved those attached to the anterior mitral leaflet. In 1 patient the chordae to the posterior leaflet were ruptured, and in the sixth patient there were ruptured chordae involving both leaflets. The common finding in the patients with the torn anterior chordae was a totally random and chaotic motion of the anterior mitral leaflet echo during diastole. There was usually a notch in the leaflet motion following rapid opening of the valve. The resultant fluttering of the valve was very coarse and could easily be distinguished from that seen in patients with aortic insufficiency. The motion could be likened to that of a flapping sail which is luffing in the wind. In the 2 patients who had torn chordae involving the posterior mitral leaflet, the posterior mitral valve echo moved markedly posteriorly during the onset of ventricular systole. The leaflet stayed posterior throughout systole and returned anteriorly with ventricular diastole. This motion was distinctly different from that seen in patients with prolapsed mitral valve in that there was no normal motion of the posterior leaflet during early systole in the patients with torn posterior chordae. Similar echocardiographic findings have not been seen in patients with other forms of mitral insufficiency. Thus, the findings seem to be specific and should be of clinical value in patients with suspected torn chordae tendineae.

Emergency Myocardial Revascularization with Saphenous Vein Bypass Graft

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The use of elective saphenous vein bypass grafting in patients with chronically disabling angina has been increasing in the past 4 years. We have also been using saphenous vein bypass grafts in patients with severe myocardial insufficiency and preinfarctional symptoms in an effort to prevent myocardial necrosis.

Eight patients, aged 43 to 61 years (mean 54 years), have undergone emergency coronary arteriography and subsequent revascularization surgery within 7 days (most within 48 hours). Three additional patients studied by coronary arteriography because of progressive angina underwent emergency surgery following a severe episode of myocardial ichemia subsequent to coronary arteriography; in 1 of these documented 100% occlusion of the right coronary artery developed during the study.

The distribution and severity of the coronary atheromatous lesions, the hemodynamic data, the surgical results and the early clinical followup data are presented. One patient died postoperatively. Five patients had single grafts, 4 had double grafts and 2 had triple grafts. Nine of 10 grafts studied postoperatively were patent; 1 graft could not be catheterized. Preoperative electrocardiographic signs of severe myocardial ischemia and dysrhythmia were almost completely reversible in all 10 surviving patients. These patients had clinical improvement with a loss of pain. Postoperative dysrhythmic complications were absent, and more extensive myocardial necrosis was avoided. Two typical case histories are also presented.

H–V Prolongation in Left Bundle Branch Block: Clinical and Electrocardiographic Correlations

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In left bundle branch block (LBBB), the H–V interval is a measure of conduction in the distal His bundle and right bundle branch. His bundle electrograms were recorded in 44 patients with LBBB to evaluate the significance of H–V prolongation. H–V was normal (NHV) in 22 (35–55 msec) and was prolonged (PHV) in 22 (57–125 msec). The average age of patients with NHV was 61 years and with PHV 64 years. Coronary disease (ASHD), diagnosed by history of angina or previous infarction, was present in 15 patients (69%) with NHV and in only 8 (37%) with PHV ($P < 0.02$). Hypertension was common in both NHV (12 patients) and PHV (16 patients). In the NHV group, the range and mean of electrocardiographic measurements were as follows: P–R interval, 0.12 to 0.24 second, mean 0.16; QRS duration, 0.12 to 0.16 second, mean 0.13; QRS axis, −60 to +90°, mean −7°. In the PHV patients the P–R interval was 0.14 to 0.48 second, mean 0.21; QRS duration, 0.12 to 0.20 second, mean 0.15; QRS axis, −60 to 60°, mean −23°. Only the differences in QRS duration were significant ($P < 0.05$).

In LBBB, the frequency of normal H–V with ASHD was consistent with localized ischemic lesions of the left bundle, whereas the frequency of H–V prolongation without ASHD was consistent with idiopathic diffuse conduction disease. QRS duration greater than 0.16 second was useful in predicting H–V prolongation (bilateral bundle branch disease).

Dysrhythmias and Conduction Defects with Pathologic Study of the Sinoatrial Node After Mustard's Operation for Transposition of the Great Arteries

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This study concerns (1) dysrhythmias after Mustard's operation for transposition of the great arteries in 60 patients who survived the operation, and (2) the histologic features of the sinoatrial (S–A) node in 5 of these who later died—2 during recovery, 1 after 4 months, 1 after 4 years and 1 after 5 years—presumably from rhythm disturbances. Only 3 patients remained in sinus rhythm at all times after the operation. The incidence of sinus rhythm postoperatively was 30% at the end of the first year and only 13% at

the end of 3 years. In 54 patients, low voltage atrial waves having the configuration of sinus P waves were seen at one time or another. The incidence of passive dysrhythmias remained nearly the same (about 50%). Many patients showed, at several times, a P axis directed downward to the right and anteriorly, consistently falling either behind the QRS with fixed R–P interval or before the QRS with fixed P–R interval. This was explained by an initial silent atrial retrograde conduction from the ectopic focus. Active dysrhythmias gradually increased. Partial or complete atrioventricular block was not seen at any time. In 1 patient type A Wolff-Parkinson-White conduction developed and persisted.

In the necropsy material from the patients recently operated upon, the S–A nodal tissue was defined in its usual position. In and about the node, fresh hemorrhage and acute inflammation surrounded the sutures. The S–A nodal artery in the 3 patients who died after 4 months or more was altered by marked intimal sclerosis and medial hypertrophy. The lumen was reduced to a mere slit. Dense connective tissue and fat occupied the usual site of the S–A node.

Regional Left Ventricular Performance in the Year Following Myocardial Infarction

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A quantitative relation between abnormal regional myocardial performance and left ventricular (LV) function has not been established in man. To determine if such a relation exists, 25 patients were evaluated 2 to 12 months after a transmural myocardial infarction (MI) by coronary and quantitative biplane angiocardiography. Abnormally contracting segments (ACS) (akinesis or dyskinesis) of the left ventricle were identified in 24 patients and their location correlated with the site of coronary artery occlusion and with the electrocardiographic location of MI. ACS were calculated in each view by dividing the akinetic or dyskinetic length of the end-diastolic ventricular perimeter by the total end-diastolic ventricular perimeter, and the average of the anteroposterior and lateral fractions was expressed as a percentage. ACS (range 1.9–60.5%) correlated with the LV ejection fraction (EF) (range 0.09–0.64) using a cubic regression equation ($r = -0.82$, $P < 0.0001$) and also using a theoretical spherical model: $EF = 0.67\left(1 - \frac{ACS}{100}\right)^3$ ($r = -0.80$, $P < 0.0001$). Patients with heart failure (paroxysmal nocturnal dyspnea or ventricular gallop, or both) demonstrated ACS (33.9 ± 15.0%) significantly larger than ACS (18.3 ± 10.5%) of patients without heart failure ($P < 0.007$).

These data demonstrate that the relative size of an abnormally contracting region of the ventricle is (1) quantitatively related to impairment of ventricular function, and (2) a significant factor in determining the presence or absence of heart failure. Furthermore, since the theoretical model assumes that the non-ACS myocardium is normal in function, the actual function of the non-ACS myocardium may be assessed by comparing the observed EF to the EF predicted for the observed ACS. A lower than predicted EF indicates that the non-ACS myocardium is abnormal in function.

The Beneficial Effects of the Combined Use of Vasoconstrictors and Intraaortic Balloon Counterpulsation in the Therapy of Cardiogenic Shock

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Although the frequent ineffectiveness of vasoconstrictors alone or intraaortic balloon counterpulsation (IABC) alone in the therapy of cardiogenic shock is well documented, their combined effects have not been delineated. Therefore, we studied the hemodynamics and myocardial energetics of 6 dogs with experimental myocardial infarction during IABC, phenylephrine infusion (PE) and combined PE + IABC.

IABC increased myocardial oxygen consumption (MVO_2), but augmented myocardial oxygen delivery (MDO_2) more, thereby improving the MDO_2/MVO_2 index 19 ± 0.9% SEM ($P < 0.05$). However, this effect was insufficient to restore normal hemodynamics. PE infused to raise mean aortic pressure (mean BP) from 58 ± 1 to 114 ± 9.5 mm Hg augmented MDO_2 considerably more than MVO_2 with a resultant improvement in the MDO_2/MVO_2 index of 61.8 ± 1.8% ($P < 0.005$). Addition of IABC produced another increase in MDO_2, coupled with a decrease in MVO_2, thereby improving the MDO_2/MVO_2 index further ($P < 0.005$). To establish whether these improvements in the MDO_2/MVO_2 index favorably affected the ischemic region, we performed 6 additional experiments in which multiple epicardial electrograms were recorded. At a mean BP of 60 ± 10 mm Hg, IABC for 1 hour had no significant effect on the area of S–T segment elevation. Elevation of the mean BP with PE to 105 ± 10 mm Hg in 1 hour produced a reduction of total ischemic electrographic changes from 5.2 ± 0.2 to 3.4 ± 0.2 mv ($P < 0.005$). Addition of IABC caused further rapid improvement, frequently abolishing all abnormalities. Discontinuation of therapy produced severe ischemic changes again. Thus, for cardiogenic shock, vasoconstrictors to increase coronary perfusion pressure combined with IABC to decrease afterload and increase diastolic coronary blood flow are preferable to either therapy alone.

The Nature of the Intrarenal Stimulus Eliciting Renal Hypertension

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Renal ischemia is often assumed to be the cause of renovascular hypertension but precise, serial measurements of renal blood flow have not been made before and after production of hypertension. Accordingly, electromagnetic flowmeters were implanted around renal arteries of 15 unanesthetized dogs, and blood flow and arterial pressure were measured daily before, for 15 days after removal of the untouched kidney and for up to 64 days after tightening a renal artery clamp. Unilateral nephrectomy caused sustained increase in flow to the remaining kidney (+71 ± 9 ml/min) without changes in arterial pressure. After mild stenosis (20% decrease in systolic flow) in 10 dogs, persistent hypertension developed within 16 days in each. Onset of the increase in blood pressure was accompanied by transient decrease in renal flow, but within days thereafter it returned to or was above the elevated values present after unilateral nephrectomy. Pulse flow (difference

between systolic and diastolic flow) was markedly diminished when arterial pressure began to increase and remained significantly diminished in each dog, even when hypertension became established and mean flow returned to control values. More severe constriction in 5 other dogs (−46% decrease in systolic flow) elicited in 4 malignant hypertension which was associated with a large decrease in mean renal blood flow that persisted until death. In 4 of the 10 dogs with mild stenosis of the renal artery, renal perfusion pressure measured beyond the site of the constriction was found always to be reduced compared with systemic pressure, even when hypertension was established and renal flow was increased. The findings indicate that a reduced renal pulse flow, or renal perfusion pressure, or a combination of both, signals the kidney to produce hypertension; gross renal ischemia apparently is not a causative factor.

Echocardiographic Determination of Mitral Valve Flow

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Reflected ultrasound was used as a method of visualizing the mitral valve leaflets in an effort to determine mitral valve flow. The mitral orifice was defined as the measured distance between the echoes from the anterior and the posterior leaflets. Normal volunteers and patients undergoing cardiac catheterization were used. Subjects exhibiting any evidence of mitral valve dysfunction were eliminated from the study. The typical mitral orifice displayed 3 distinctive components: (1) an initial diamond-shaped, rapid filling phase followed by (2) a low amplitude, rectangular phase and, finally, (3) a short diamond-shaped atrial component. A mitral valve index (MVI) was derived by taking the sum of the products of the maximal amplitude and duration of the individual components. In 25 normal subjects the MVI was compared with simultaneous stroke volume (SV) determinations derived from echocardiographic left ventricular internal dimensions. A close correlation was noted between these 2 measurements (r = 0.90, P <0.001, SEE = ±2 ml). In 13 patients who underwent cardiac catheterization, the MVI was compared with the SV obtained using the Fick method on a subsequent day. Again, the relation between the MVI and SV was highly significant (r = 0.88, P <0.001, SEE = ±14 ml). This empirical method of determining mitral valve flow appears to be reasonably accurate in patients without mitral valve dysfunction. Its potential clinical and investigative usefulness as a noninvasive technique of measuring mitral valve flow and left ventricular stroke volume is promising.

Postural Changes in Left Ventricular and Mitral Valvular Dynamics in the Systolic Click–Late Systolic Murmur Syndrome

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Marked changes in the auscultatory pattern with posture have been noted in patients with midsystolic clicks (MSC) or late systolic murmurs (LSM), or both. MSC tend to move earlier in systole, and LSM become longer and often louder when patients assume upright posture. Systolic prolapse of the mitral leaflets with mild regurgitation accounts for MSC–LSM; earlier and greater prolapse with more and prolonged regurgitation associated with a reduced left ventricular (LV) volume in the upright position would explain the auscultatory changes.

Seventeen patients with MSC–LSM were studied supine and at 45° head-up tilt. Intracardiac pressures, cardiac outputs and systolic time intervals were recorded, and LV cineangiography was performed. Four patients without mitral valve disease and 3 with severe mitral regurgitation were similarly studied for comparison. The hemodynamic responses to tilt were similar in all 3 groups. Of the patients with MSC–LSM, systolic prolapse of one or both mitral leaflets was demonstrated in all. LV volume was decreased at 45° in all 9 technically satisfactory studies. Greater mitral prolapse was noted with patients upright in 6 of 8 studies with enough sinus beats to judge. The amount of mitral regurgitation was mild in all, and changes in amount from supine to upright posture could not be discerned angiographically. Hypotension on passive tilt complicated 8 of the 24 studies and tended to diminish the auscultatory changes. The findings suggest that the auscultatory changes occurring with upright posture in patients with MSC–LSM are related to greater prolapse of the mitral leaflets which is associated with a smaller LV volume in the upright position.

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Reduced Subendocardial Blood Flow and Ventricular Contractile Force Caused by Nitroglycerin

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The effects of both intracoronary (IC) and intravenous (IV) administration of nitroglycerin (NTG) on transmural distribution of blood flow in the left ventricle after partial coronary artery occlusion was investigated using 2 independent methods. In 16 open chest anesthetized dogs, tubing supplying the cannulated left coronary artery was partially occluded. Strain gauges sutured parallel to superficial and deep fibers of the myocardium separately recorded the contractile force (CF) of each layer (as described previously from this laboratory). With occlusion set so that depression of the deep CF was imminent, 12 μg IC NTG in 7 dogs depressed only the deep CF without changing systemic hemodynamics. IV administration of 180 μg NTG in 9 dogs resulted in a decrease of deep CF and aortic pressure often associated with an increase in superficial CF. Distribution of myocardial blood flow during peak coronary flow after IC or during a decrease in aortic pressure following IV NTG administration was determined by the tissue uptake of an IC bolus of ^{86}rubidium. This was compared to the uptake of ^{42}potassium injected before NTG. IV or IC administration of NTG caused a significant reduction in subendocardial blood flow with a decrease in the subendocardial/subepicardial ratio of isotope.

These experiments suggest that under conditions of acute partial coronary occlusion the autoregulatory response results in more fully dilated subendocardial vessels which are less responsive to NTG. NTG may

then reduce the vascular resistance in the subepicardial more than the subendocardial vessels, resulting in a "steal" of blood flow from deep to superficial myocardium with little or no change in total coronary flow.

Acute Myocardial Infarction: Myocardial Perfusion and Metabolism

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Coronary blood flow (CBF) and myocardial metabolism were evaluated in 26 patients with coronary artery disease. Ten subjects had stable coronary artery disease, 5 were hospitalized with acute coronary insufficiency without infarction and 13 had acute myocardial infarction (AMI) (2–96 hours after infarct). In the AMI group, 5 patients had uncomplicated infarction, 5 had congestive heart failure and 2 had cardiogenic shock. CBF was measured by the thermodilution coronary sinus flow technique, and transmyocardial arteriovenous differences of lactate, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, creatine phosphokinase, potassium, magnesium and calcium were determined. Although lactate metabolism at rest was abnormal in 8 of 12 with AMI, CBF in patients without shock (127 ± 16 cc/min, range 71–218 cc/min) and coronary vascular resistance (6.3 ± 0.9 × 10^4 dynes sec cm^{-5}) did not differ from values in the groups without infarction. Furthermore, no significant difference in arterial and coronary sinus levels of electrolytes or enzymes was found in the AMI group despite the presence of rising serum enzyme levels. The levels of CBF in the AMI patients did not correlate well with any individual determinant of flow (arterial diastolic pressure, left ventricular (LV) filling pressure, LV $\Delta P/\Delta T$, or heart rate). Thus, despite definite evidence of reduced regional myocardial perfusion and necrosis, total CBF remained normal and did not decrease with increasing size of infarct. The absence of detectable enzyme and potassium leakage in the presence of abnormal lactate metabolism suggests that (1) the rate of release of these substances is slow relative to the sensitivity of current methods of biochemical analysis, and (2) metabolic studies in AMI may be seriously limited by this phenomenon.

On the Mechanism of Diastolic Rumbles

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We used the combined techniques of phonocardiography, apex cardiography and mitral valve echocardiography in simultaneous multichannel recordings to study the apical diastolic rumbling murmur accompanying the following conditions: pure mitral regurgitation (MR, no. = 7); severe aortic regurgitation (AR, no. = 16); large left to right shunt (no. = 2); and mitral stenosis (no. = 12). In patients with MR, shunt or AR the rumbles were indistinguishable phonocardiographically and occurred in mid-diastole after the period of rapid ventricular filling. In these patients the rate of mitral valve closure was excessively rapid, and the murmur occurred as the valve was closing. In patients with mitral stenosis in normal rhythm the crescendo portion of the presystolic murmur occurred after the period of atrial systole. In patients with mitral stenosis and atrial fibrillation a crescendo presystolic murmur occurred when the duration of the preceding diastole was short. In both cases the crescendo murmur was coincident with the closing movement of the mitral valve. This occurred after the onset of isometric ventricular systole.

Our findings suggest that these murmurs are due to increasing flow velocity as a result of a dynamically narrowing mitral valve orifice. The increase in flow velocity may occur even when the volume of flow is diminishing. A common denominator is thus demonstrated in the genesis of diastolic rumbling murmurs in a variety of conditions.

Improved Left Ventricular Function During Nitroprusside Infusion in Acute Myocardial Infarction

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Afterload is a major determinant of myocardial oxygen consumption (MVO_2) which, if decreased, should benefit an ischemic myocardium and improve ventricular performance. In 11 patients with acute myocardial infarction (AMI) nitroprusside (NP), a potent vasodilator, was infused at a rate sufficient to produce a slight reduction in arterial pressure (AP). During NP infusion mean AP decreased from an average of 106 to 87 mm Hg, whereas heart rate was unchanged. Left ventricular filling pressure (LVFP) decreased consistently from an average of 21.6 to 10.0 mm Hg ($P < 0.01$). In 6 patients with clinical signs of left ventricular failure or shock and cardiac index (CI) less than 2.5 liters/min per m^2, cardiac output (CO) and stroke volume increased during NP infusion by an average of 1.21 liters/min (41.5%) and 16.5 ml/beat (47.8%), respectively ($P < 0.025$). In patients with control CI greater than 2.5 liters/min per m^2, CO was not significantly changed during NP infusion. A fall in pressure time per minute (2,840 to 2,327 mm Hg sec/min, $P < 0.025$) as well as the decrease in LVFP indicated a reduction in MVO_2 during NP infusion. With careful dose manipulation, a decrease in LVFP and rise in CO often could be attained without a significant fall in AP.

These data suggest that administration of NP reduces aortic impedance and results in an increased stroke volume from a reduced LVFP and a presumed lower MVO_2 in patients with low cardiac output complicating AMI.

The Normal Blood Supply to the His Bundle and Proximal Bundle Branches

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Ten human hearts without coronary disease were injected with a highly colored barium gelatin mass to outline the blood supply to the His bundle (HB) and proximal bundle branches (PBB). A different color was injected into right (R), left anterior descending (LAD) and circumflex coronary arteries. The coloring material can withstand histologic processing and permitted histologic determination of the blood supply to these structures. The HB received a dual supply of blood from the atrioventricular nodal artery (AVNA)

and penetrating branches from the anterior septum in 90% of cases. The HB and PBB were supplied wholly by AVNA in 10%. The proximal right bundle branch and anterior fascicles of left bundle branch (LBB) received a dual supply in 50% and were supplied by anterior septal branches alone in another 40%. The posterior fascicles of the LBB received a blood supply from the AVNA in 50% and a dual supply from AVNA and anterior septal arteries in 40%. In 10% the posterior fascicles were supplied by the LAD. We conclude that the blood supply to most portions of the HB and PBB is frequently dual, with the most anterior and posterior portions being commonly supplied by the anterior septal and AVN arteries, respectively. These 2 vascular systems generally arborize in the mid-portion of the HB.

New England Regional Infant Cardiac Program

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A regional program encompassing all 11 New England hospitals which provide definitive care for infant cardiac patients was begun in 1969. The purposes of this program are to increase case finding, to encourage early referral and to improve transportation, diagnosis and treatment. Data referrable to any infant ill with cardiac disease have been tabulated and results covering a 36 month period (circa 1,200 infants) will be available within weeks.

To date experience with 826 critically ill infant cardiac patients seen between July 1968 and June 1970 is available. During the first year of program activity 457 babies underwent cardiac catheterization or cardiac surgery or died, compared to 369 in the prior year. Three hospitals managed 70% of the infants; 30% were managed in 8 smaller hospitals. Overall hospital mortality for the 2 year period was 36%. Whereas 115 patients underwent surgical procedures (29% mortality) in 8 smaller hospitals, an additional 31 babies were transferred to larger hospitals for surgery. Among the larger hospitals gross surgical mortality was 40% (32–56%). Medical management of 455 patients resulted in 36% mortality. The hospital using surgical treatment most aggressively (54% surgical management) produced the lowest overall mortality rate (32%); the hospital that used conservative treatment most often (55% medical management) produced the highest overall mortality rate (49%). From these preliminary experiences, it is our impression that an aggressive approach to case finding, early diagnosis and treatment results in improved survival among infants critically ill with cardiac disease.

Alterations in the Left Ventricular Contractile State During Isometric Exercise in Patients with Coronary Artery Disease

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The effects of isometric exercise (IE) on myocardial function were evaluated in 8 patients. Two normal subjects and 6 patients with angiographically documented coronary artery disease (CAD) were studied before and at 3 minutes of IE (25% maximal voluntary contraction). Using isovolumic pressure measurements (SF-1, catheter tip micromanometer), contractile element velocity (V_{CE} = [dp/dt]/24P in sec^{-1}) at 0 load (Vmax) and peak V_{CE} were derived. Left ventricular (LV) max dp/dt, heart rate (HR), blood pressure (BP), and arteriovenous oxygen (A–V O_2) differences were measured.

During IE all 8 patients had similar increases in HR (22%) and mean BP (18%). In 2 normal subjects and 1 patient with CAD, LV end-diastolic pressure (EDP) and A–V O_2 differences remained unchanged; Vmax increased 38% (2.1 ± 0.2 to 2.9 ± 0.3), peak V_{CE} increased 43% (1.6 ± 0.2 to 2.3 ± 0.2), and max dp/dt increased 22%. In 5 patients with CAD the A–V O_2 difference widened 12% (4.1 ± 0.3 to 4.6 ± 0.2 vol %), LVEDP increased 69% (16 ± 3 to 27 ± 6 mm Hg) and max dp/dt increased 16%. In this group, Vmax averaged 1.6 ± 0.1 and peak V_{CE} averaged 1.1 ± 0.2 (control state); during IE there was no change in Vmax or peak V_{CE} in 3 of the 5; angina developed in the other 2, and in both patients Vmax and peak V_{CE} fell (18% and 20%, respectively).

Thus, it appears that in normal subjects LV performance improves during IE by a shift to an augmented ventricular function curve (improved contractile state, no change in perload), whereas in some patients with CAD this transition does not occur (increased preload, no change in contractile state). When angina occurs preload increases and a decrease in contractility may occur. IE, as a test of myocardial function, has been used to gain further insight into altered ventricular dynamics in patients with CAD.

Manifest and Concealed Reentry: A Mechanism of Atrioventricular Nodal Wenckebach in Man

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Previous explanations of the atrioventricular nodal (A–VN) Wenckebach phenomenon have centered around the concept of decremental conduction. Recent animal studies from this laboratory suggest that A–VN reentry may provide an alternate mechanism of conduction delay and block during A–VN Wenckebach cycles. The present study documents similar findings in man.

Four patients were studied using electrograms recorded from the high right atrium (HRA) and His bundle (HBE) during stimulation of the atrium (A) and ventricle. During sinus rhythm, a normal sequence of atrial depolarization from high (HRA) to low (HBE) atrium was noted. Ventricular pacing (S) was associated with a reversal of atrial depolarization. In addition, a retrograde His (H_R) was seen in 2 patients. The ventricle was paced at a cycle length sufficient to produce retrograde Wenckebach. At a critical degree of retrograde A–VN delay, manifest reentry (reciprocal beat) occurred. Decreasing the cycle length of stimulation concealed the reentry. The presence of concealed reentry can be confirmed by noting an antegrade His deflection with a shorter S–H interval than the otherwise constant S–H_R during ventricular pacing. Both concealed and manifest reentry occurred after the last retrograde atrial complex of the Wenckebach cycle. The mechanism by which the last ventricular impulse

of the Wenckebach cycle is blocked retrograde is due to a collision of the reentrant and the retrograde wavefronts. A similar mechanism may explain antegrade Wenckebach.

Failure of Intracoronary Nitroglycerin to Alleviate Pacing-Induced Angina

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To assess the role of the direct effects of nitroglycerin (NTG) on the coronary circulation in the relief of angina, NTG was injected after induction of angina by pacing into the left (LCA) or right coronary artery (RCA); the doses were too small to cause a significant decrease in arterial blood pressure but in normal subjects were sufficient to augment coronary sinus blood flow (CSBF) by 50 to 100% for 30 to 60 seconds. After insertion of the angiographic catheter into the LCA, angina was induced by pacing from the coronary sinus at a previously determined threshold rate in 11 patients. A dose of 0.05 to 0.1 mg NTG in 1 ml of 5% dextrose was then injected into the LCA. If the intensity of angina did not decrease or was increased, the pacing was discontinued after 1 minute. Arterial blood pressure, lead V_5 and coronary sinus blood flow by thermodilution were recorded continuously. In 7 patients the same procedure was repeated with injection into the RCA. In none of the patients did the injection of NTG into either coronary artery alleviate angina in spite of a significant increase in CSBF in 4 of them. NTG was ineffective whether injected into the obstructed artery or into the artery supplying collateral vessels to the obstructed artery. In 3 patients the injection of NTG into the LCA was followed after 60 seconds by intravenous injection of 0.3 mg NTG. The latter caused a significant decrease in blood pressure and in 1 to 2 minutes relieved the pain unaffected by the preceding intracoronary injection. The results indicate that the direct effects of NTG on the coronary arteries play little, if any, role in this agent's antianginal action, which appears to be due entirely to the reduction of myocardial oxygen requirements, secondary to the agent's effects on the systemic circulation.

Electrophysiologic Properties of Atrial and Ventricular Muscle from Cats with Experimentally Induced Heart Failure and Hypertrophy

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Previously, we noted characteristic changes in ventricular electrical properties after chronic partial pulmonary arterial (PA) occlusion. To evaluate the role of altered electrical properties in development of right heart failure (RHF) and ventricular hypertrophy (RVH), we monitored action potentials (AP) and isometric force (P) of atrial and ventricular muscle from normal, sham operated, RHF and RVH cats. Chronic right ventricular systolic hypertension produced by PA occlusion was followed by RVH and RHF. For right atrial and right ventricular muscles from RHF cats, resting potential (RP), AP amplitude, AP rate of rise, P and dP/dt were decreased compared to values in control muscles. Epinephrine and acetylcholine (ACh) increased RP, AP amplitude, AP rate of rise and P in failed atrial muscles, whereas ACh increased RP but decreased P in normal atrial muscles. These data indicate that depressed RP, AP amplitude and conduction may exacerbate the contractile defect in RHF. Right ventricular muscles removed from hearts (without failure) 1 day after PA banding had normal electrical and mechanical properties. Right ventricular muscles removed from hearts (without failure) 3 days after PA banding had depressed P and dP/dt; electrical properties were normal except AP plateau was shifted to more negative potentials. Shift in level of AP plateau voltage was less for right ventricular muscles from 7 day bands. AP plateau voltage level was normal for right ventricular muscles 21 and 90 days after PA banding although P was still decreased. Altered voltage level for AP plateau may affect voltage-dependent contractile events and thus P in early stage of hypertrophy.

Thirty-Two Cases of Interventricular Septal Defect and Aortic Insufficiency: Clinical, Hemodynamic and Surgical Features

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Thirty-two cases of interventricular septal defect (IVSD) with aortic insufficiency (AI) are reported, in 20 of which operations were performed. The aortic insufficiency was generally slowly progressive in those patients in whom this could be determined. A right ventricular subpulmonic valvular gradient was found in 45% (13 patients), and in about half of these (6 patients) the gradient was due to prolapse and herniation of the right aortic cusp through the IVSD. This is a much higher incidence than has been appreciated. Of the 20 patients operated upon, none had aortic valve replacement, 6 had accompanying annuloplasties and 14 had IVSD closure only. In none was the aortic insufficiency made worse, and in only 5 was the AI definitely not benefited. In 3 cases of IVSD closure only, the AI completely disappeared postoperatively, and in at least 4 others the AI was significantly reduced in severity. It is concluded that patients with this combination of lesions should be considered for early closure of the IVSD in order to prevent progressive AI.

Augmentation of Contractility Following Ischemia in the Isolated Supported Heart

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Catecholamine-mediated increases in contractility have been observed immediately following release of coronary artery occlusion, an effect sometimes attributed to local release of myocardial norepinephrine stores. However, previous studies have not excluded the possibility that this inotropic effect may depend upon neural or humoral mechanisms. We therefore examined the influence of ischemia on contractile performance of completely isolated, working canine hearts. Coronary perfusion was maintained using arterial blood from a

donor dog. Ischemia was produced by occlusion of the perfusion line for varying lengths of time. After release, coronary sinus effluent was temporarily diverted to a reservoir to ensure total isolation of the preparation. Contractility was assessed by measuring pressure (P) and rate of pressure rise (dp/dt) in a left ventricular balloon. In each of 10 hearts, restoration of coronary perfusion pressure to base-line value resulted in prompt rise in peak P and dp/dt above pre-ischemic values. Percentage overshoot above base-line value increased with longer ischemic periods up to a mean maximum of 73% ± 24 SD in peak P observed after 60 to 150 seconds of ischemia. Propranolol produced dose-related attenuation in extent of overshoot after ischemia, indicating that overshoot in contractility is mediated by beta receptors. In contrast to contractility, heart rate changed little either during or after ischemia. Our data confirm the hypothesis that brief periods of coronary occlusion provoke subsequent enhancement of contractility in ischemic regions due to local release of myocardial catecholamines. This enhancement is not dependent upon systemic hemodynamic or neural alterations that may accompany myocardial ischemia.

Correlation of the Antiarrhythmic Effects of Diphenylhydantoin with Digoxin-Induced Changes in Myocardial Contractility, Sodium–Potassium-Dependent Adenosine Triphosphatase and Potassium Efflux

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To clarify the suppressant action of diphenylhydantoin (DPH) on digitalis-induced arrhythmias we studied the effects of DPH and digoxin, alone and in combination, on myocardial contractile force (CF), sodium–potassium dependent adenosine triphosphatase activity (N–KA) and K^+ efflux in Krebs-Ringer perfused dog hearts. Neither control perfusion nor perfusion with DPH alone (3×10^{-5} M) altered N–KA or produced K^+ efflux. Perfusion with DPH alone depressed CF. Perfusion with digoxin alone (10^{-6} M) caused a mean 59% rise in CF at onset of toxicity (repetitive ventricular extrasystoles) along with net K^+ efflux averaging 50 ± 12 μmoles/min and decrease in average N–KA from 13.8 to 5.2 μmoles phosphate/mg of protein per hour ($P < 0.001$). Adding DPH to the digoxin perfusion delayed toxicity an average of 13 minutes (or 82%), at which time CF was higher, mean 91% above control ($P < 0.05$), K^+ efflux greater (mean 87 ± 20 μmoles/min) and N–KA lower (mean 2.5, $P < 0.05$) than with digoxin alone. However, combined DPH-digoxin perfusion interrupted at the time toxicity appeared with digoxin alone yielded higher N–KA (mean 7.7, $P < 0.02$) and less rise in CF (mean 26% above control, $P < 0.05$). Thus DPH appeared to reduce the extent of N–KA inhibition induced by digoxin in a given time period. Nevertheless, DPH ultimately permitted digoxin to produce greater increase in CF, greater K^+ efflux and greater N–KA inhibition than possible without DPH. These data suggest that the antiarrhythmic efficacy of DPH in treating digitalis toxicity cannot be attributed solely to prevention of inhibition of N–KA or to diminution of K^+ efflux, 2 potentially arrhythmogenic changes characteristically accompanying digitalis administration.

Hemodynamic Changes Accompanying Exertional Syncope in Dogs with Right Ventricular Outflow Obstruction

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Several mechanisms have been postulated to be responsible for the exertional syncope seen with ventricular outflow obstruction, but the precise hemodynamic events leading to this form of syncope are largely unknown. To study exertional syncope more closely, 7 dogs with acute right ventricular outflow obstruction (produced by inflation of a previously implanted pulmonary arterial balloon cuff) were exercised to syncope. Right ventricular and systemic arterial pressures (AP) as well as the electrocardiogram were recorded continuously. During 6 syncopal episodes (in 3 dogs) recordings also were obtained from an electromagnetic flowmeter previously implanted about the ascending aorta. In every dog syncope was preceded by a rapid decrease in AP (from an average of 100 to 39 mm Hg). This decrease was never the result of an ectopic rhythm disturbance. Sinus tachycardia (average heart rate 249 beats/min) occurred before decline in AP and during the early hypotensive phase. However, in the 10 seconds immediately preceding syncope, heart rate fell an average of 27 beats/min ($P < 0.005$). The precipitous decrease in AP was accompanied both by a 48% reduction in cardiac output ($P < 0.005$) and by a 23% decrease in peripheral resistance ($P < 0.05$). Recovery of consciousness and restoration of AP usually occurred before cuff deflation. Our results demonstrate that, under the conditions studied, arrhythmia is not a primary cause of exertional syncope. Furthermore, the rapid reduction in AP that leads to syncope is caused not only by a decline in cardiac output, but also by vasodilatation of the systemic arteriolar bed.

Sudden Death and Hospitalization Delay in Acute Myocardial Infarction

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The relation between factors affecting delay in hospitalization and those affecting sudden death were studied in 98 patients experiencing an acute myocardial infarction in an industrial population (median age 55 years). All patients experiencing an acute myocardial infarction over a 10 month period were studied. The mortality rate was 26% (26/98), and 84% (22/26) of the deaths were sudden, occurring within 1 hour. Two sudden deaths occurred in transit and 4 occurred in an emergency facility. Sudden death occurred in 6 of 26 patients (23%) whose symptoms began at work and in 16 of 72 patients (22%) whose symptoms began away from work. Nineteen of the 22 sudden deaths were witnessed. Nineteen of the patients who died within 1 hour had a history of angina pectoris, acute myocardial infarction or prodromal symptoms. In the 78 patients who survived to admission, the effect of

these same factors on arrival time at the medical facility was studied. The mean arrival time for the group was 285 ± 39 minutes. The mean arrival time for patients with angina was 465 ± 125 minutes, for those with prodromal symptoms 381 ± 83 minutes, and for those with a history of acute myocardial infarction was 259 ± 73 minutes. Thus, patients with a history of angina or prodromal symptoms had a prolonged arrival time and those with a history of acute myocardial infarction did not shorten their arrival time. In this population sudden death was the overwhelming event of acute coronary mortality. The same factors that appear to predispose to sudden death also result in a prolonged arrival time, thus suggesting that although death due to acute myocardial infarction may be sudden, it does not occur without warning.

The Transition from Double Outlet Right Ventricle to Complete Transposition. A Pathologic Study

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Ninety-four heart specimens of complete transposition of the great vessels (TGV) and 40 of double outlet right ventricle (OBGRV) were studied. Correlations were made with embryonic developments involving the conotruncus in 54 normal human embryonic hearts. The conal septum is identically completely inverted and the great vessels are identically interrelated in TGV, OBGRV and Taussig-Bing anomaly. The conal septal inversion is probably due to lack of counterclockwise torsion of the ostium bulbi during the formation of the loop of the heart tube. The riding position of the pulmonary artery (PA) over the left ventricle (LV) differs almost from one case of OBGRV to another. In specimens with OBGRV with the PA arising only from the right ventricle (RV), leftward shift of the conoventricular flange did not occur. In those with Taussig-Bing anomaly, in which the PA mostly rides over the LV, a "normal" leftward shift of the conoventricular flange probably occurred. Intermediate positions of the PA account for the great variety of patterns of OBGRV. The absence of pulmonary conus, and the presence of pulmonary mitral fibrous continuity, is a characteristic feature of TGV. It is assumed that absorption of the pulmonary conus obliterates the conus tunnel (subpulmonic ventricular septal defect) and brings the PA to the mitral valve, thus transforming the Taussig-Bing anomaly to TGV. Photomicrographs of the conotruncal torsion and the conus absorption will be shown, and photographs of heart specimens showing the spectrum of anomalies leading from OBGRV to TGV will be demonstrated.

Cardiac Effects of a Cocktail

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The hemodynamic effects of a cocktail during cardiac disease is unknown. Ten patients with cardiac disease and 4 normal subjects underwent cardiac catheterization. Hemodynamic measurements were obtained before and 30 minutes after oral ingestion of 2 ounces of Canadian Club whiskey. In the 10 abnormal subjects the average cardiac index decreased with alcohol from 3.3 to 2.7 liters/min per m^2, the stroke index decreased from 41 to 33 ml/beat per m^2, the arteriovenous oxygen difference increased from 4.9 to 6.2 vol %, the left ventricular end-diastolic pressure increased from 10 to 12 mm Hg, and the pulmonary arterial mean pressure and cardiac rate were unchanged. In the 4 normal subjects the average cardiac index increased with alcohol from 3.2 to 4.5 liters/min per m^2, the stroke index increased from 49 to 68 ml/beat per m^2, the pulse rate increased from 79 to 80 beats/min, and the arteriovenous oxygen difference decreased from 4.5 to 3.4 vol %. With alcohol all of the patients with cardiac disease demonstrated a fall in the cardiac index and stroke index. In the normal subjects, alcohol produced an increase in these indexes. The different hemodynamic response in the 2 groups was statistically significant ($P < 0.02$). Small amounts of alcohol can impair cardiac function in patients with cardiac disease.

Occlusive Coronary Disease in the Transplanted Denervated Heart: Assessment by Exercise Electrocardiogram and Coronary Arteriography

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Since January 1968, 34 cardiac transplant operations have been performed at Stanford, and 14 patients are presently alive. Actuarial statistics show 45% survival at 1 year, 30% at 2 years and approximately 30% at 3 years. Since patients with denervated hearts would not be thought to experience angina pectoris as a manifestation of ischemia, routine exercise electrocardiography has been performed regularly, in an attempt to diagnose ischemic changes in all long-term survivors of transplantation. Correlation with hemodynamic studies and coronary arteriography has been performed at yearly intervals. Four patients with normal exercise studies have had completely normal coronary arteriograms and hemodynamic status at 1 year. Two other patients have had abnormal exercise electrocardiograms. One had a positive test at 28 months, with S–T segment depression and ventricular ectopic beats. Coronary arteriography showed a blocked left circumflex artery, and cardiac catheterization showed a poor exercise response. The other had a positive exercise electrocardiogram at 35 months, and this correlated with diffuse small vessel disease on the coronary arteriogram. Both patients remain asymptomatic and have never had angina. All other survivors have negative exercise studies.

Long-term cardiac transplant survivors are susceptible to the development of occlusive coronary artery disease without evidence of chest pain. These changes can be reliably detected by exercise electrocardiography and confirmed by coronary arteriography.

Results of Early Surgical Repair of Ventricular Septal Defects Following Myocardial Infarction

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A ventricular septal defect (VSD) occurring as a complication of acute myocardial infarction has been associated with a poor prognosis if treated medically. Surgical closure of the defect, if carried out at least 6

weeks after infarction, results in a 30% 1 year survival rate, as published reports show. To date, surgical repair attempted within the first 2 weeks has been associated with a prohibitively high mortality rate. At Stanford, 10 patients (age range 55–74 years) have undergone emergency surgical closure of the defect within an average of 8 days after infarction, and 5 days after the appearance of VSD. Each patient had refractory cardiogenic shock following the sudden onset of the typical findings of a VSD. The diagnosis was confirmed preoperatively by an oxygen step-up in the right ventricle. Surgical repair in each case involved closure of the defect with a Teflon® patch supported in place by mattress sutures and Teflon felt pledgets, in addition to resection of an associated ventricular aneurysm in 2 patients. Five patients died within 1 week after surgery. The other 5 patients remain clinically well an average of 14 months (range 7–43 months) after surgery. Residual shunts are present in 2 patients.

This small series shows that successful surgical treatment of ventricular septal defects can be accomplished within 2 weeks after infarction. The 1 year survival rate of 50% compares favorably with the results of elective repair of VSD's occurring after infarction.

The Role of Platelet Aggregation in Catecholamine-Induced Cardiac Necrosis: Electron Microscopic and Drug Studies

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To determine if the cardiac necrosis seen after catecholamine infusion in experimental animals might be due to platelet aggregation in the capillaries of the heart (catecholamines cause platelet aggregation in vitro), studies (1) using drugs known to inhibit platelet aggregation and (2) using electron microscopic methods were undertaken. In 1 study, 30 dogs were infused with epinephrine (4 μg/kg per min). Ten were pretreated with aspirin, 10 grains twice daily (A) for 4 days, 10 pretreated with dipyridamole, 50 mg twice daily (D), and 10 served as control dogs. All dogs had a significant increase in blood pressure during infusion. The dogs were killed 1 week later, and sections of the myocardium were studied histologically with necrosis graded 0 to +++. All control dogs had cardiac necrosis; 5 +++, 3 ++ and 2 +. Seven of the 10 dogs treated with A and 7 of the 10 treated with D had no necrosis (P <0.01). One dog pretreated with D had ++, 1 had + and 1 trace necrosis; 3 dogs treated with A had + necrosis. In another study, 4 dogs were infused with norepinephrine, 4 μg/kg per min for 4 hours. At the end of the infusion they were killed, and cardiac sections were studied with the electron microscope. In all dogs capillaries were found that contained platelets adherent to the walls and to each other. Numerous capillaries were completely occluded by platelet thrombi with and without interspersed fibrin. The endothelium of the capillaries was damaged in some instances, but intact in others, thus suggesting that the aggregation of platelets was primary and not secondary to wall injury.

It is concluded that platelet aggregation in capillaries plays a significant role in the production of cardiac necrosis by catecholamine infusion. This demonstration that platelet aggregation can be induced in blood vessels by catecholamines in vivo raises the possibility that the relation between stress and coronary atherosclerosis may be through catecholamine-induced aggregation of platelets on vascular endothelium serving as the nidus for the development of atherosclerotic plaques.

Left Ventricular Function Following Successful Aortocoronary Vein Bypass

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A previously published report suggested that successful aortocoronary vein bypass surgery is accompanied by improvement in left ventricular performance. This question was reexamined using standard hemodynamic and biplane angiocardiographic techniques. Pre- and postoperative results are available in 11 consecutive patients who had single (2), double (9), or triple (1) vein grafts which were patent at the time of restudy. After operation, angina was completely relieved in all patients. Values for left ventricular end-diastolic pressure (13 ± 5–11 ± 6), end-diastolic volume (81 ± 17–77 ± 12), stroke volume (44 ± 12–39 ± 9) and systolic ejection fraction (SEF) (55 ± 12–51 ± 7) were not significantly changed after surgery. Neither patients with normal SEF (5) nor those with depressed SEF (6) demonstrated significant postoperative changes. We were unable to confirm an improvement in ventricular performance and believe that aortocoronary surgery preserves rather than improves ventricular performance.

Alterations in Renal Vascular Resistance Following Coronary Artery Occlusion in Dogs

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Since acute myocardial infarction with hypotension and cardiogenic shock appears to be infrequently associated with acute tubular necrosis (ATN), accounting for only 19 of 1,731 cases of ATN in several large series, it seemed pertinent to study the behavior of the renal vascular bed during experimental coronary artery occlusion (CAO). Both initial reflex responses and subsequent alterations in total renal vascular resistance (RVR) were evaluated (total 33 dogs) during CAO. An innervated, constant blood flow, perfused kidney preparation was used, which incorporated a delay circuit in the perfusion tubing so that any initial changes (up to 120 seconds) in RVR following CAO could only be of reflex origin. In all animals, CAO resulted in a mean decrease in systemic arterial pressure (SAP) of 27.8 ± 2.3% SEM. Despite this, the reflex response of the renal vascular bed was vasodilatation in 18 of 23 dogs. Mean RVR decreased 7.4 ± 2.4% (P <0.005). CAO was maintained for 11 or more minutes in 10 dogs. Reflex and persistent renal vasodilatation occurred in 7, whereas only 1 showed reflex and persistent vasoconstriction. The mean response of these 10 was persistent renal vasodilatation (P <0.05). In contrast, hemorrhage for brief periods (10 dogs), resulting in the same degree of decrease in SAP as CAO, was associated with an average increase in RVR of

12.0 ± 3.6% ($P < 0.005$). In addition, ventricular fibrillation in every animal resulted in marked, immediate reflex increases in RVR. Following beta adrenergic blockade (propranolol) in 10 dogs, CAO resulted in initial reflex vasodilatation, but this was followed by later vasoconstriction ($P < 0.05$). The anticipated response to reduced SAP is that of reflex vasoconstriction through baroreceptor mechanisms. In these animals, the capacity for the renal vascular bed to vasoconstrict reflexly was demonstrated by 2 different stimuli. In spite of this, the response of the renal vascular bed to CAO was that of vasodilatation. Although these data were obtained in anesthetized animals and represented only short periods of study, they appear to be significant as regards the demonstration of paradoxical reflex responses.

Dopamine in the Treatment of Refractory Cardiogenic Shock

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Dopamine, a precursor in the biosynthesis of norepinephrine, has been shown previously to have potent inotropic actions when administered in small doses, while producing little change in heart rate and blood pressure. This agent was administered in 32 instances to 28 patients with cardiogenic shock who were refractory to other forms of therapy. Therapeutic benefit was noted at doses as low as 2 μg/kg per min, but in some patients the administration of 20 μg/kg per min was required to maintain a prolonged benefit. The drug was administered for more than 24 hours to 15 patients in this series. The blood pressure increased in 22 of 32 patients and increased to greater than 90 mm Hg systolic in 11. Urinary output was increased significantly in 19 of 32 patients, and to greater than 50 ml/hour in 12. The clinical response was judged to be good in 18 patients. In 2 patients ventricular arrhythmias developed, limiting the dose which could be administered, and 2 others had prolonged chest pain associated with an increase in blood pressure produced by dopamine. Other side effects were minimal. It is concluded that dopamine in small doses produces hemodynamic improvement in many patients with refractory cardiogenic shock. With larger doses, its circulatory effects can be maintained for long periods, and when tachyphylaxis develops, increases in the dose may continue to produce beneficial effects.

Experimental Atrial Fibrillation in Conscious Dogs

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Studies were undertaken to study cardiac performance in conscious dogs with atrial fibrillation (AF). Dogs were fitted with instruments under aseptic technique, with left ventricular internal diameter, left ventricular pressure cells, left atrial pressure, aortic pressure cells, electrodes were placed into left atrial and ventricular walls for measurement of left atrial and ventricular electrograms, respectively. Atrial fibrillation was produced through atrial stimulation at high frequency. AF was studied before and during periods of infusion with norepinephrine, glucogen, atropine SO_4, propranolol and before and after digitalization with ouabain. AF was analyzed using serial autocorrellogram and the mean square spectral density analysis of total cycle lengths. The latter revealed that in AF there are 2 discrete peaks which shift to the right with norepinephrine activity and to the left with digitalization. These data tend to support the findings of Moe et al., of the presence of a nonrandom phenomenon, most likely due to concealed conduction. However, these data tend to counter the hypothesis of Bootsma et al. that the ventricular irregularities seen in AF are due to randomly spaced atrial impulses of random strength reaching the atrioventricular node from random directions. Evidence is presented which shows that myocardial contractility is continually changing from beat to beat during AF.

The Correlation of S–T Segment Elevations and Axis Shifts in Graded Treadmill Exercise Tests with Coronary Arteriographic Findings

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To determine the relation between coronary arteriographic findings and S–T segment elevation or axis shifts after exercise, the treadmill tests of 158 patients who had had coronary arteriograms were reviewed. Occlusion of the right, left main, anterior descending and left circumflex arteries was graded on a scale of 0 to 4. All 5 patients with S–T segment elevation in leads II, III and aVF had severe arterial disease with no specific arterial predominance and no uniform changes on the resting electrocardiogram (ECG). All 12 patients with S–T segment elevation in the precordial leads had severe disease of the anterior descending artery, but only 6 had anterior myocardial infarction on resting ECG. Thirteen patients had significant axis shift after exercise. Four of 9 with right axis shift and 3 of 4 with left axis shift had severe arterial disease, but there was no specific arterial predominance in either group. Of 108 patients with no axis shift, 73 had severe arterial disease.

Conclusions: (1) Post-exercise S–T segment elevation in the precordial leads was associated with severe coronary artery disease, particularly in the left anterior descending artery; (2) post-exercise S–T segment elevation in leads II, III and aVF was associated with severe coronary artery disease, but without predominant involvement in any specific artery; (3) right axis shift was not associated with an increased incidence of coronary artery disease and (4) left axis shift was associated with severe coronary artery disease in 3 of 4 patients, but its significance is unclear because of small group size.

Myocardial Glycogen Content and Myocardial Function During Anoxia

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Cardiac glycogen is known to be a substrate for glycolysis during cardiac anoxia. The following study was designed to assess a possible protective effect of increased myocardial glycogen stores in the anoxic working heart.

Two groups of dogs were studied; those in group I (6 animals) were restricted to a fat diet for 3 days before study, and those in group II (5 control animals)

were fed a routine maintenance diet. Following controlled ventilation with oxygen (100%) and left thoracotomy for monitoring of left atrial, left ventricular and aortic pressures, ascending aortic blood flow and left ventricular contractions by an epicardial mercury gauge, the animals were ventilated with nitrogen (100%) for 5 minutes and subsequently with O_2 (100%) during recovery. Serial biopsy specimens taken from the apex of the left ventricle were immediately frozen and later analyzed for glycogen by an anthrone method. pH, blood gases, electrolytes and catecholamine levels were measured, and left ventricular dp/dt, work, index of contractility, tension-time index and peripheral arterial resistance were determined.

Animals in group I were found to have significantly elevated myocardial glycogen levels (1,456 ± 190 μg/100 g heart muscle) as compared to those in group II (732 ± 150 μg/100 g heart muscle). After 5 minutes of breathing nitrogen and during recovery, group I demonstrated a significantly greater ($P < 0.01$) decrease in myocardial glycogen than did group II. After 1 minute of anoxia dp/dt was significantly higher ($P < 0.05$) for group I than for group II. Myocardial glycogen utilization was observed to correlate closely with left ventricular dp/dt and with left ventricular work during and after anoxia. These observations support the concept that increased levels of myocardial glycogen may be beneficial to the heart during brief periods of anoxia.

Near Miss "Pseudo-Complications" of Cardiac Catheterization

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Cardiac catheterization (Cath) procedures may be associated with serious complications, even when performed in a technically flawless fashion. This prospective study investigated complications preceding (and not caused by) cardiac catheterization over a 12 month period. All complications that occurred in the 48 hours *preceding* the scheduled catheterizations were termed "near miss pseudo-complications." A total of 1,036 diagnostic catheterizations were performed in this period.

There were 26 (2.6%) near miss pseudo-complications, including 12 (1.2%) sudden deaths in patients (mean age 63) who were scheduled for *but who had not yet undergone Cath.* These included myocardial infarction (6), asystole, ventricular tachycardia or fibrillation (5), cerebrovascular accident (3), peripheral arterial occlusion (3), pulmonary embolization (1), cardiac rupture with tamponade (1), severe congestive heart failure (1), cardiogenic shock (2) and sudden death for unknown reasons (4). Four additional patients died while awaiting admission to the hospital for possible Cath. There were 26 (2.6%) major complications, including 6 (0.6%) deaths (mean patient age 52) which occurred soon after the 1,036 Caths were performed.

Similar complications were noted in both groups of patients, both catheterized and uncatheterized, during this period of time. Twice as many deaths occurred in those awaiting Cath. The incidence of "complications" would have doubled and the mortality rate tripled if the procedure had been performed up to 48 hours earlier in the 26 patients in the near miss group. The incidence of complications after Cath is materially influenced by the chance occurrence of complications resulting from a severe disease process.

Angiographic Analysis of Left Ventricular Performance in Patients with Rheumatic Mitral Stenosis

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Recently it has been suggested that impaired left ventricular performance is frequent in patients with rheumatic mitral stenosis (RMS). Accordingly, in 9 patients with pure RMS, 5 biplane, 2 frontal and 2 lateral cineangiocardiograms were obtained. In each patient 2 to 8 beats were analyzed and compared. Ejection fraction (EF) and the mean rate of circumferential fiber shortening (MRFS) at the minor left ventricular equator were calculated for each beat; in 3 patients with atrial fibrillation average values were obtained. EF ranged from 0.33 to 0.61 in 5 patients and was abnormal (<0.51) in 3. The MRFS in the frontal projection ranged from 0.52 to 1.70 circumferences (circ)/sec and was consistently abnormal (<1.2 circ/sec) in 2 of 7 patients. In the lateral projection MRFS ranged from 0.43 to 4.52 circ/sec and was consistently impaired in 5 of 9 patients. The EF and MRFS were concordant in 14 beats and discordant in one or both projections in 7 contractions. No patient had a normal MRFS in both projections in all analyzed beats. Six patients underwent successful mitral commissurotomy and are in class I and II (New York Heart Association) 1 month to 2 years after operation. We conclude that impaired left ventricular mechanical performance is common in patients with pure RMS but that these abnormalities may not be related to prognosis after operation.

Prediction of Acute Changes in Left Atrial Hemodynamics from the P Wave

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Earlier studies have shown that sudden changes in hematocrit or volume of end-diastolic blood mass will profoundly alter beat to beat QRS configuration. To evaluate this effect on the P wave, packed cell infusion or hemodilution was carried out in 13 dogs, while spatial magnitudes were measured from a 24 electrode grid. By varying resistivity over a range from 67 to 671 ohms/cm (ρ) a linear relation between (ρ) and peak spatial magnitude of the P wave ($r = 0.89$, $P < 0.001$) was shown.

Pulmonary capillary wedge (PCW) pressures were monitored with Swan-Ganz flow-directed catheters for several days in 32 patients admitted to the coronary care unit. Electrocardiographic P terminal forces (PTF) from lead V_1 were correlated in 91 instances with simultaneous PCW. PTF correlated significantly with PCW ($r = 0.82$). If PCW exceeded 12 mm Hg, PTF was always abnormal, that is, less than −0.030 mm sec. Sequential changes of PCW and PTF were

concordant in 46 instances. It appears that acute P wave alterations provide a useful, serial assessment of acute hemodynamic dysfunction of the heart.

Electrocardiographic Localization of Injury in Acute Myocardial Infarction: Relation to Left Ventricular Function and Cardiac Pump Failure

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The relation of electrocardiographic (ECG) location of cardiac damage to ventricular function and clinical course was evaluated in 143 patients with acute myocardial infarction (AMI). AMI's were classified by ECG as anterior (Ant), inferior (Inf) or anterior-inferior (Ant-Inf). Hemodynamic assessment revealed striking depression of ventricular function in Ant-Inf compared to Ant and Inf ($P < 0.01$); stroke work index (SWI)—Ant-Inf, 21.2 g-m/m^2; Ant 30.1; Inf 29.1. Further evaluation by 2-point ventricular function curves (obtained by tilt or fluid infusion) differentiated ($P < 0.01$) Ant from Inf: Inf—pulmonary arterial wedge pressure (PAW) 7.5 to 15.5 mm Hg, SWI 27.3 to 40.1 g-m/m^2 (+49%); Ant—PAW 7.2 to 14.9 mm Hg, SWI 28.9 to 32.1 g-m/m^2. Cardiogenic shock occurred in only 7% of Inf (4 of 56 patients), 20% of Ant (14 of 70 patients, $P < 0.01$), and 53% (8/15 patients, $P < 0.01$) of Ant-Inf. Likewise, mortality was similarly related to location of AMI: Inf 29%, Ant 35%, Ant-Inf 69%. Therefore, location of AMI by ECG correlates with hemodynamic aberration and provides an indication of prognosis. Inf is associated with relatively greater preservation of myocardial function than Ant, and Ant-Inf is particularly associated with ventricular dysfunction and severity of clinical course.

Disseminated Intravascular Coagulation Complicating Severe Congestive Heart Failure

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The syndrome of disseminated intravascular coagulation (DIVC) has received increasing attention in the past few years. Although DIVC often occurs under conditions in which regional blood flow is reduced (i.e., shock of any origin), reports of DIVC complicating congestive heart failure (CHF) are rare. This low incidence may be more apparent than real, since we recently studied 10 patients with severe CHF who manifested DIVC. Diagnosis of DIVC was based on platelet count, presence of circulating fibrinogen degradation products, prothrombin time, thrombin time, partial thromboplastin time, factor V and factor VIII levels and bleeding time. Severity of DIVC was variable, ranging from marked thrombocytopenia in 1 patient (who had 70 g of fresh thrombus in the left atrium at operation) to mild transient thrombocytopenia in another. Clinical deterioration accompanied DIVC in all patients, and evidence of pulmonary embolic disease was noted in 8 of 10. Resolution of DIVC followed intensive medical therapy alone in 6 of 10, and open heart surgery in 3 of 10. One in-hospital fatality occurred. Our results thus indicate that DIVC is not rare in patients with severe CHF, that it may be associated with pulmonary embolic episodes or intracardiac thrombi, and that it appears to be reversible in most patients with adequate medical or surgical treatment of CHF.

Intravascular Hemolysis and Thrombocytopenia in Left Ventricular Outflow Obstruction

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Despite considerable interest in intravascular hemolysis (IH) in valvular heart disease, no studies thus far have dealt with red cell and platelet survival in isolated discrete aortic stenosis (AS) and muscular left ventricular outflow obstruction (IHSS) of wide severity. Catheterization was performed in 20 cases: 11 of valvular AS; 2 of nonstenotic bicuspid aortic valves (BAV); 1 of discrete congenital subvalvular AS; and 6 of IHSS. All subjects had hematocrit, reticulocyte, platelet and megathrombocyte counts, haptoglobin, lactic dehydrogenase and Coombs tests, urine hemosiderin and peripheral blood smears; 17 had ^{51}chromium red cell survivals, 3 plasma hemochromagens and 8 bone marrow aspirations. Intravascular hemolysis was classified as isolated decrease in ^{51}Cr survival and compensated or uncompensated hemolytic anemia; platelet disorders were classified as isolated increase in megathrombocytes with or without thrombocytopenia.

Of patients with valvular AS, 6 had IH (gradients 52–140 mm Hg), 4 had no IH (gradients 30–54, mild AS or severe with heart failure), 4 had increased megathrombocytes, 3 with and 1 without thrombocytopenia. The single patient with discrete subvalvular AS had IH with normal platelets, gradient 55. Both patients with nonstenotic BAV had IH, 1 with increased megathrombocytes. Of the patients with IHSS, 4 had IH with decreased platelets. We conclude that in discrete AS, IH is more likely in severe AS before failure; platelet disorders correlate poorly with gradients. Previously unreported IH and platelet disorders were found with both unobstructed BAV and with IHSS.

The Effects of Lidocaine on Refractory Periods in Man

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The refractory periods (RP) of the atrium, atrioventricular node (A–VN) and ventricular specialized conduction system (VSCS) were studied in 10 men using His bundle recordings and the extra stimulus method. Measurements were made during fixed atrial pacing to eliminate the effect of changing preceding cycle length on refractoriness. After these values were obtained, a bolus of lidocaine (1 mg/kg) was given followed by an infusion of 1 mg/min. The refractory periods were then restudied over the next 30 to 45 minutes.

Lidocaine significantly shortened (>30 msec) the RP of the atrium 30 to 70 msec in 5 of 9 patients, and in only 1 patient did the atrial RP increase. The RP of the A–VN was not significantly influenced by lidocaine, and in the 2 patients in whom the RP of the VSCS could be measured it was not altered. However, in all patients in whom an RBBB–LAH pattern of aberrant

conduction developed during premature depolarization lidocaine shortened the relative refractory period, i.e., reduced the H_1–H_2 interval at which aberration occurred. In addition, after lidocaine 1 patient exhibited RBBB–LPH at the same H_1–H_2 interval that previously demonstrated RBBB–LAH. In 1 patient aberration was totally prevented.

These results indicate that lidocaine might be useful in some reentrant atrial tachyarrhythmias. In addition, the lack of appreciable effect on the RP of the A–VN and VSCS confers on lidocaine relative safety in the management of arrhythmias in the presence of various degrees of atrioventricular block or ventricular conduction defects.

Echocardiographic Diagnosis of Left Atrial Thrombi

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Systemic emboli, consequent to left atrial thrombosis, constitute a serious complication of rheumatic heart disease, and their recognition could be of considerable clinical value. We have studied 41 patients with mitral stenosis with echocardiographic techniques, directing the beam of ultrasound through the aortic root or the left ventricle into the left atrial chamber. Four patients had findings suggesting the presence of left atrial thrombus, and in each of these the diagnosis was later confirmed by cineangiography and subsequent cardiac surgery. The echocardiographic findings noted were (1) increased thickness of a portion of the posterior left atrial wall; (2) a mass projecting into the left atrial cavity; and (3) decreased movement of a portion of the left atrial wall. These ultrasound findings were not noted in the remaining 37 patients with mitral stenosis, and cineangiography and cardiac surgery in 24 of these revealed no thrombi were present. These findings differ from those seen in atrial myxoma, which are mobile tumors and do not produce the same posterior wall abnormalities.

This study indicates the usefulness of echocardiography as a noninvasive method for detecting left atrial thrombi in patients with rheumatic heart disease. This technique should facilitate decisions regarding anticoagulation and suggest the optimal means of approaching the left atrium during cardiac catheterization or surgery.

Role of Blood Pressure in the Development of Congestive Heart Failure: The Framingham Study

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A representative population sample of 5,192 men and women was followed up for 16 years; during this time 142 persons had overt congestive failure (CF). In the age range 30 to 62 years the dominant etiologic precursor was hypertension, which preceded failure in 75%. Hypertensive subjects had 6 times more CF than normotensive subjects.

Examination of the risk of myocardial hypertrophy on X-ray film and electrocardiogram according to antecedent systolic versus diastolic pressure revealed little to suggest a greater role for diastolic pressure. Discriminant analysis failed to show a stronger net effect for diastolic pressure. Both systolic and diastolic pressure, the mean arterial pressure, the pulse pressure and tension-time index discriminated potential hypertrophy and failure no better than systolic pressure alone. Examination of the regression of heart weight and left ventricular thickness at autopsy on premorbid systolic versus diastolic pressure revealed slopes with similar gradients and a better correlation with systolic than diastolic pressure. CF was a lethal phenomenon with only 50% surviving 5 years. Early, vigorous and sustained control of essential hypertension—systolic as well as diastolic—would appear the chief means for preventing CF in the general population.

Effects of Varying End-Diastolic Volume and Inotropic State on Ventricular Performance During Atrial Fibrillation in Man

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A study of the influence on ventricular performance of variations in end-diastolic volume (EDV) compared with alterations in inotropic state due to abrupt cycle length change has not been adequately performed in man. Accordingly, in 10 patients with atrial fibrillation (AF), 65 beats were analyzed by cinangiocardiography. In each, arterial pressure, R–R interval, EDV, ejection fraction (EF), and the mean rate of circumferential fiber shortening (MRFS) at the minor left ventricular equator were measured. The length of the preceding diastolic filling period correlated well with the subsequent change in EDV ($r = 0.65$, $P < 0.001$). The latter bore a significant relation to the change in EF ($r = 0.70$, $P < 0.0001$) and MRFS ($r = 0.52$, $P < 0.0001$) from the previous beat. The ratio of the prepreceding to the preceding cycle length (RR_1/RR_2) was used to measure the relative degree of abrupt cycle length change. This ratio was then utilized as an index of myocardial inotropic state, since over a wide range it could be demonstrated in 3 patients with AF that as RR_1/RR_2 fell, Vmax rose. Changes in RR_1/RR_2 also correlated with alterations in the succeeding EF ($r = -0.69$, $P < 0.001$) and MRFS ($r = -0.47$, $P < 0.01$). These data indicate that in man beat-to-beat alterations of left ventricular performance in AF can be related not only to variations in ventricular filling (Frank-Starling mechanism) but also to changes in the inotropic state of the heart. The results also suggest that single measurements of EF and MRFS in patients with AF may not be representative of overall left ventricular performance.

The Collateral Venous Circulation After Glenn Anastomosis

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Clinical deterioration occurs late after Glenn anastomosis and is characterized by increasing cyanosis and decreasing exercise tolerance. Fifteen children with tri-

cuspid atresia or common ventricle were examined 4 to 8 years after a satisfactory superior vena cava–right pulmonary artery shunt. All patients had initial palliation to various degrees then later deterioration. They were studied with biplane selective angiography with injections into the left ventricle and left subclavian vein. All patients showed development of collateral venous circulation which in the presence of an open anastomosis limited effective shunt flow by stealing blood from the right lung through the following channels: (1) Oblique vein of Marshall which may have predated the shunt as a patent left superior vena cava or, more frequently, developed patency in a vestigial channel. Both drain to coronary sinus. (2) Other systemic drainage including internal mammary tributaries, hemi-azygous system, and pericardial and thymic veins. Most patients revealed additional compromise of circulation to left pulmonary artery in the form of closure of atrial or ventricular septal defect or acquisition of pulmonary atresia. These patients were treated by ligation of the venous collateral vessel and creation of an additional systemic to pulmonary artery shunt. The importance of programmed restudy of children after Glenn anastomosis by venous angiography and left ventriculography is stressed.

S–T Segment Isolation as a Means of Improving Diagnostic Accuracy in Treadmill Stress Testing

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Treadmill stress testing is limited in its diagnostic capacity by electrocardiographic artifact, observer variation, and upward sloping S–T segments in both normal persons and patients with coronary artery disease (CAD). With use of computer analysis, a method of S–T segment isolation (IST) has been developed which identifies patients with CAD even in the presence of upward sloping S–T segments. Maximal exercise was performed by 151 subjects on a treadmill; speed and slope were increased every 3 minutes. Signals from a bipolar chest lead were averaged repeatedly over 10 second intervals. The S–T segments were electrically isolated from the T waves, and ISTs were quantified with regard to slope, magnitude and integral of depression. Group I comprised 62 normal control subjects; Group II comprised 35 patients with unequivocal clinical or coronary angiographic evidence, or both, of CAD and typically abnormal stress tests ($\geq$ 1 mm flat or downsloping S–T segments); Group III comprised 54 patients with CAD and normal or nondiagnostic stress tests by standard inspection. IST integral values of -6.0 to -10.0 μv-sec (depending on heart rate) separated Groups I and II. With these criteria, 40 of 54 patients in Group III were correctly identified as having CAD. Only 3% false positive and 17% false negative results were observed. We conclude that determination of the isolated S–T segment integral facilitates diagnosis of ischemia during treadmill testing, improves diagnostic specificity and sensitivity, and is preferable to simple visual inspection of the exercise electrocardiogram.

Ineffectiveness of Prophylactic Atropine in Decreasing Arrhythmias and Enhancing Survival Following Acute Coronary Artery Occlusion in Conscious Dogs

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Sudden death occurring shortly after acute myocardial infarction (AMI) probably results from ventricular fibrillation (VF). Since increased heart rate (HR) suppresses some ventricular arrhythmias, self-administration of atropine at onset of AMI has been advocated as a measure to reduce AMI mortality. To test this hypothesis, AMI was produced in 55 conscious, closed chest dogs by inflation of a balloon cuff previously implanted around the left anterior descending coronary artery (LAD). Ten minutes after occlusion, 28 dogs were treated with atropine, maintaining HR between 90 and 120/min. After 1 hour occlusion was released for 10 minutes and "release arrhythmias" recorded. The LAD was then reoccluded 2 more hours. The results are shown in Table I.

A significantly greater incidence of ventricular arrhythmias occurred during occlusion in the atropine-treated animals. Although release arrhythmias and sudden death (VF) also occurred more often in the treated group, this trend was not statistically significant. Moreover, arrhythmias, including VF, occurred more frequently ($P < 0.05$) in dogs that had *spontaneously* fast heart rates ($\geq$85/min) after 10 minutes of occlusion. We conclude the following: (1) Slow heart rates following experimental AMI are associated with a decreased risk of developing arrhythmias and sudden death than higher rates; and (2) atropine tends to increase the incidence of arrhythmias during AMI. If these results are applicable to man, routine administration of atropine may be not only without benefit but deleterious in some patients with AMI.

TABLE I

Results

Animals	Occlusion Arrhythmias	Release Arrhythmias	VF (Death)
Control	48%	64%	18%
Atropine-treated	93%*	88%	39%

* $P < 0.01$.

Twenty-Four Hour Left Ventricular Bypass in the Unanesthetized Dog: A Study Employing Transthoracic Cannulation and a Paracorporeal Roller Pump

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A series of dogs were prepared for left ventricular bypass by suturing 1 end of a 12 mm Dacron® graft to the unopened wall of the left atrium and burying the other end in the subcutaneous tissue. Several days later, the left atrium was cannulated with a no. 28F silicone rubber mushroom catheter. This catheter was held taut by a sharp stylet and was introduced through

the Dacron graft during positive pressure ventilation. The mushroom catheter was connected to the inflow line of a small air-driven roller pump. Pump output was delivered into the divided ends of the left carotid artery. The animals stood in a supportive sling after pumping had been initiated. The dogs breathed room air.

Ten dogs underwent successful left ventricular bypass for 24 hours. The mean flow rate during bypass was 62 ml/kg per min, the mean arterial pressure was 113 mm Hg immediately after starting pumping, and 88 mm Hg at the termination of pumping. The mean plasma hemoglobin determination after bypass was 71 mg/100 ml. Upon termination of bypass, the catheters in the left atrium and in the left carotid artery were removed and the overlying skin was closed. One week after bypass the dogs were sacrificed. The punctured wall of the left atrium was found to have healed well. This study indicates the feasibility of temporary long-term left ventricular bypass in the dog. We believe that the technique of transthoracic cannulation, when properly employed, is a safe method of introducing a large caliber catheter into the left atrium.

The Evolution of Coronary Arterial Pathology in Patients with Angina Pectoris as Determined by the Coronary Arteriogram

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The progression of coronary artery disease (CAD) was determined by repeat coronary arteriography in 48 patients with typical angina pectoris. Thirty-eight patients were male and 10 were female; their ages averaged 48.8 years. The average interval between arteriograms was 22.5 months. The total patency of the coronary arteries was graded as 300, with each of the 3 main vessels scoring 100. The lesions were measured as percent of total lumen obstruction.

There were 2 groups of patients. Group A comprised 37 patients, 3 of whom had significant disease in a single vessel, 5 had 2-vessel and 29 had 3-vessel disease in the initial study. On the repeat arteriogram, findings in 2 of 3 patients with single vessel disease remained unchanged. The third had a 7% increase in total lumen obstruction. Findings in 5 patients with 2-vessel disease were unchanged, but 4 of this group had a 21.4% increase in total obstruction. Twenty-five of the 29 patients with 3-vessel disease had an increase in total lumen obstruction of 13.3%; in 4 obstruction was unchanged. There were 26 coronary arteries noted to have only lumenal irregularities. In only 4 instances was progression to significant obstructive lesions noted in the second arteriogram. Group B comprised 11 patients with angina pectoris who had no coronary disease on either examination.

In patients with significant coronary disease, there was a 13.8% average increase in total coronary lumen obstruction in 22.5 months. Because of the degree of disease present initially, this increase could have material clinical effect. In addition, those patients who had no coronary disease initially remained free of disease despite a clinical history of typical angina pectoris.

Myosins from Right and Left Ventricle: Comparison of Adenosine Triphosphatase Activities and Substructure

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To examine the possibility that the dissimilar mechanical conditions under which the mammalian right (RV) and left (LV) ventricles contract might be reflected in differences in their contractile proteins, the adenosine triphosphatase (ATPase) activities and light fragments of myosins from rat RV and LV were compared. Variations in these myosin characteristics might be expected in view of findings that skeletal muscles serving different physiologic functions have myosins that differ in both enzymatic activity and substructure.

Yields of actomyosin-free myosin from RV and LV were similar. No differences in magnesium-activated (0.013 μmoles/min per mg) or calcium-activated (0.11 μmoles/min per mg) ATPase activity were noted. These activities were, however, significantly higher than those of pooled RV–LV canine cardiac myosin, prepared and studied under similar conditions. Light fragments prepared from RV and LV with 8M urea appeared to be identical when separated by polyacrilamide gel electrophoresis in sodium dodecylsulfate and mercaptoethanol.

Notwithstanding differences in both afterload and dynamic geometry during the cardiac cycles of RV and LV, myosins from both ventricles of the rat appear to be identical. The higher level of ATPase activity of rat cardiac myosin, compared with canine cardiac myosin, is consistent with evidence that cardiac maximal shortening velocity (Vmax) is greater in the rat, and thus supports the view that a property of myosin determines the Vmax of a muscle.

"Pacing" Left Ventricular Function Curves in Conscious Dogs

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In seeking to determine the efficacy of using "pacing" ventricular function curves, obtained from conscious instrumented animals, as one means of evaluating ventricular performance changes that might occur in them as a result of some experimental intervention, observations have been made of the effects of atrial, ventricular and sequential pacing in dogs. The left atrium and ventricle were paced for short periods at 2, 2.5, 3 and 3.5 Hz using bipolar electrodes. Then sequential pacing using an atrial systole-ventricular systole of 95 msec was used. The animals were instrumented so as to permit simultaneous recordings of dLnP/dt, dP/dt, aortic, left ventricular and atrial pressures, left ventricular internal diameter and the left ventricular electrocardiogram. The recording of these primary variables permitted the calculation for each of a series of cardiac cycles, derived variables such as left ventricular volumes, stroke work, total peripheral resistance, stroke power, cycle lengths and a variety of other variables. A small digital computer and A to D converter was used for the on-line data acquisition and reduction. End-diastolic volume stroke work function curves were constructed using the data derived from the stepwise

atrial pacing. It was observed that V_{CE} (muscle lengths/sec) increased systematically with each increase in heart rate during atrial pacing. This was not seen with either ventricular or sequential pacing. The function curves were straight as opposed to the usual curvilinear character shown by Sarnoff et al. These "pacing" ventricular function curves were shifted to the left during periods of norepinephrine infusion and to the right after beta blockade with propranolol. Sequential pacing provides usable left ventricular function curves in conscious instrumented dogs, and the use of this type of "pacing ventricular function curve" as one way to evaluate ventricular performance in man seems valid.

Electrical Impedance Cardiogram. Measurements from Hearts with Acute Injury

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Electrical impedance cardiograms were made from 35 consecutive patients entering the coronary care unit and from 10 normal control subjects daily for 3 days. Impedance changes were recorded by passing a 50 kHz current at constant voltage through the horizontal plane of the thorax at the level of the usual electrocardiographic lead sites. Changes in amperes inversely indicated changes in impedance, according to Ohm's law. We have earlier shown that these impedance changes are related to functions of the heart. Impedance recordings were examined for evidence of acute injury, using the following criteria derived from studies of normal subjects and of patients after heart surgery: (1) mean impedance above 158 ± 33 ohms; and (2) beat-to-beat variation in the configuration of the scalar impedance tracings. The tracings during each of 4 consecutive cardiac cycles differed from the others. Thirty-three patients had acute myocardial ischemia or acute infarction, and their mean impedance reached a maximum of 486 ± 203 ohms. This was significantly higher than in the control subjects ($P < 0.01$). Thirty-one patients had regular sinus rhythm and had acute ischemia or acute infarction. Twenty-eight of these 31 patients with acute myocardial injury showed beat-to-beat variation in their impedance cardiograms. Tracings from the normal subjects showed no beat-to-beat variation ($P < 0.01$). These studies show that in patients with acute myocardial injury the mean transthoracic impedance is higher, and cardiac cyclical impedance changes are grossly more variable than in normal subjects.

Refractoriness of the Accessory Pathway and Mechanisms of Reentry in the Wolff-Parkinson-White Phenomenon

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Atrial (A), His bundle (H) and ventricular (V) electrograms were recorded by electrode catheters in 12 patients with the Wolff-Parkinson-White phenomenon. In 6, the pattern of A–V conduction of premature atrial test impulses (PI) was determined as they were introduced progressively earlier in the atrial cycle, during sinus rhythm and fixed-rate atrial pacing. In all patients, the preexcitation pattern normalized at coupling intervals of 300 to 350 msec (median 320 msec), associated with prolonged A–H intervals. At shorter intervals of 260 to 320 msec (median 280 msec), block occurred in both the A–V node and accessory pathway (AP).

With closely coupled PI, reentrant phenomena (echoes, supraventricular tachycardia) were observed in 3 patients. The mechanism of reentry utilized the AP in a retrograde fashion in 1 patient and the A–V node alone in 2 patients. The extra stimulus method allowed the functional refractory period of the AP to be determined. Conduction delay in the AP occurred when PI engaged the AP before the latter completely recovered. In all 6 patients, the functional refractory period of the AP was greater than that of the A–V node, thus accounting for the normalization observed.

Evidence for the Direct Effects of Adrenergic Drugs on the Cerebral Vascular Bed

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Despite considerable research, the question of whether adrenergic drugs exert direct effects on the cerebral circulation has remained unresolved. With the development of a method for monitoring continuously the entire cerebral blood flow (CBF) to 1 hemisphere in the unanesthetized goat, we have been able to study this problem directly. The effects of epinephrine (E), norepinephrine (N) and isoproterenol (Iso) were investigated in 30 experiments in which an electromagnetic flowmeter had been implanted previously on the internal maxillary artery, which, in the goat, provides the sole blood supply to a hemisphere. A chronically implanted catheter in the temporal artery permitted close intra-arterial injection of drugs directly into the cerebral circulation. Both E and N (0.1 to 5.0 μg) produced dose-dependent reductions in CBF, a decrease of 55 ± 3% SEM occurring with the highest dose. These reductions occurred 8 to 12 seconds before any detectable changes in systemic pressure or heart rate. Alpha receptor blockade of the ipsilateral hemisphere with phenoxybenzamine (500 μg) totally or partially abolished this cerebral vasoconstriction. Iso (0.01 to 1.0 μg) produced dose-dependent increases in CBF, an increment of 75 ± 6% occurring with the highest dose. These increments preceded detectable systemic effects by 10 to 15 seconds. Beta blockade with propranolol (200 μg) totally or partially abolished the cerebral vasodilation induced by Iso. Thus, E, N and Iso exert powerful direct effects on the cerebral circulation of the unanesthetized goat, and these effects are mediated by alpha and beta receptors.

Role of Adrenergic Inotropic Stimuli in the Systolic Temporal Responses to Exercise

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To investigate mechanisms determining the systolic temporal responses to exercise (Ex), we measured systolic time intervals, cardiac output (CO), heart rate (HR) and arterial pressure before and 30 seconds after

a 4-minute step test. Nineteen patients with angina and 19 age-matched normal controls performed the test twice, once without and once during beta adrenergic blockade by alprenolol, 200 mg orally, a dose that blocked the effects of isoproterenol, 2.5 μg/min intravenously. Left ventricular ejection time and Q–S_2, the interval from the Q wave to the second heart sound, were corrected for heart rate as $LVET_c$ and $Q2_c$. Alprenolol did not change the responses of CO to Ex in either group but significantly diminished the shortening of preejection period and increase of HR produced by Ex in the group with angina. In normal subjects Ex before alprenolol shortened $Q2_c$ 19 ± 4 msec ($P < 0.001$) without changing $LVET_c$ but, after alprenolol, failed to shorten $Q2_c$ and prolonged $LVET_c$ 19 ± 4 msec ($P < 0.001$). In patients with angina, Ex failed to change $Q2_c$ and caused the same lengthening of $LVET_c$, 27 ± 5 msec ($P < 0.001$), both before and after alprenolol.

Thus, beta-adrenergic blockade converts normal responses of $LVET_c$ and $Q2_c$ to Ex into abnormal responses but, in angina patients, does not affect these responses, which are already abnormal. These results indicate that the normal responses of $LVET_c$ and $Q2_c$ to Ex depend on adrenergic inotropic stimuli. Furthermore, in patients with angina, failure of $Q2_c$ to shorten and marked prolongation of $LVET_c$ with Ex reflect the inability of ischemic left ventricles to respond adequately to these adrenergic inotropic stimuli.

The Effects of Ouabain and Diphenylhydantoin on Myocardial Potassium Balance in Man

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Arterial (A) and coronary sinus (CS) plasma potassium concentrations were studied continuously using an automated sampling technique in 33 patients who were free of heart failure and who were not receiving cardiac drugs. During sampling 14 patients received ouabain, 0.01 mg/kg intravenously (IV), 12 received diphenylhydantoin (DPH), 250 mg IV, and 7 received both drugs, DPH being administered 14 minutes before ouabain.

During a 14 minute control period there was no significant difference between the A and CS K^+ in the 3 groups. Ouabain caused a significant negative A–CS K^+ difference beginning within 4 minutes and lasting 18 minutes. The peak difference occurred 6 to 8 minutes after ouabain with an A K^+ of 3.78 ± 0.27 mEq/liter and a CS K^+ of 3.99 ± 0.27 mEq/liter ($P < 0.001$). Left ventricular (LV) dp/dt increased after ouabain (1,346 to 1,544 mm Hg/sec, $P < 0.001$) as did systolic ejection rate index (122.8 to 131.0 ml/sec per m^2, $P = 0.05$). Heart rate (HR), brachial artery mean pressure (BAP), LV end-diastolic pressure (LVEDP) and cardiac index (CI) did not change. Following DPH there was no change in A or CS K^+. LV dp/dt fell transiently from 1,133 to 1,009 mm Hg/sec ($P < 0.001$). HR, BAP, LVEDP and CI did not change. In the patients receiving both drugs, DPH did not prevent either the myocardial K^+ loss or the rise in LV dp/dt following ouabain. These observations in man are compatible with theories of digitalis action which associate inotropic effect with inhibition of membrane sodium- and K^+-activated adenosine triphosphatase, and suggest that the action of DPH on the myocardium is not mediated by this enzyme.

Correlation of the Computer Quantitated S–T Response to Exercise with the Arteriographic Location of Coronary Artery Disease

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The S–T segment response to graded treadmill exercise was quantitated by digital computer in 85 patients with angina pectoris and cineangiographically demonstrated coronary artery disease. All patients had a stenosis of one or more major coronary arteries of 75% or greater. Each patient was exercised until the onset of chest pain and the electrocardiogram was recorded on analog tape using a modified bipolar V_5 lead system. All patients had a normal resting electrocardiogram with this lead system. Twenty-five consecutive QRS complexes from the end of exercise and from the immediate and 3-minute recovery periods were averaged with a digital computer, and the depression and rate of rise of the ST segment were quantitated. The S–T segment response was then judged to be positive or negative using previously determined criteria.

Seventy (83%) of the patients studied had a positive S–T segment response. Of the 15 with a negative response, 11 had isolated disease of the right coronary artery (RCA) or the left circumflex artery (LCA). The incidence of a positive response was as great in isolated left anterior descending (LAD) disease as in 2- or 3-vessel disease. In the patients with a positive S–T response, the quantitated S–T changes were as great in isolated LAD disease as in LAD plus RCA or LCA disease, or both, and were significantly greater than those in patients with RCA plus LCA or isolated RCA or LCA disease. These findings suggest that the bipolar V_5 lead systems commonly used in treadmill exercise testing are more sensitive to ischemia arising from disease of the LAD artery and that additional vertical axis lead systems may increase the sensitivity of treadmill exercise testing.

Correlation of Degree of S–T Segment Depression During Exercise with Presence and Type of Coronary Artery Collaterals

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The ability of coronary artery collaterals to protect the myocardium against ischemia as reflected by S–T segment depression during exercise was studied. Treadmill exercise testing and selective coronary cineangiography were performed on 36 patients with angina pectoris and a normal resting electrocardiogram. The exercise-induced changes in the depression and slope of the S–T segment were quantitated with a digital computer, and the degree of S–T change was correlated with the presence of coronary collateral circulation and whether the collaterals were of the intercoronary or bridge type. The quantitated S–T segment changes were expressed in terms of an S–T index, giving equal weight to the slope and depression of the S–T segment. The larger the S–T index the greater the degree of segmental S–T

depression. Patients with no demonstrable collaterals (11 patients) had an S–T index of 1.58. Patients with grade 1 intercoronary collaterals (13 patients) had an S–T index of 1.55. In patients with bridge collaterals (12 patients) the S–T index was significantly less at 0.98. This finding suggests that bridge collaterals reduce the degree of myocardial ischemia during exercise in coronary artery disease, whereas intercoronary collaterals offer no appreciable protection.

Survival Experience in Saphenous Vein Bypass Graft Surgery

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Survival rates of 309 patients operated upon between March 1968 and June 1970 utilizing saphenous vein bypass graft are presented with followup data to January 1, 1971. Survival of hospitalization for surgery was required for inclusion in the group of 1 month survivors (OMS). Long-term attrition in survival rate (LTAS) through successive 6-month intervals after surgery was tabulated. OMS for the group was 86%, with a 3% LTAS. In groups categorized by assessment of ventricular contractility using left ventricular angiography, the OMS varied: normal contractility (NC), 95%; mild generalized impairment of contractility (MIC), 89%; localized single wall impairment (SWIC), 88%; localized double wall impairment (DWIC), 70%; diffuse impairment (DIC), 74%; and aneurysm (A), 56%. OMS improved from 82% during the first year of surgical experience to 89% during the second year. LTAS for the entire group was 3% and by subgroups was NC, 1%; MIC, 0%; SWIC, 6%; DWIC, 0%; DIC, 4%; and A, 15%.

The data suggest that patients symptomatic with angina without previous myocardial infarction (MI) or with only 1 previous myocardial infarction may be surgical candidates with acceptable OMS. A second infarction can be critical since these patients have more advanced ventricular impairment and greatly decreased operative survival. LTAS is encouraging at this point particularly in patients with relatively well preserved ventricular contractility. LTAS will be updated to January 1, 1972.

Factors Influencing Intercirculatory Mixing in Complete Transposition of the Great Arteries

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Hemodynamic data from catheterization of 100 patients (all more than 1 year of age) with transposition of the great arteries (TGA) were analyzed. Intercirculatory mixing, calculated as effective pulmonary flow index (EPFI), was compared in 25 patients with atrial septal defect (ASD) only (group 1), 35 patients with ventricular septal defect (VSD) only (group 2), and 40 patients with anatomic communications at 2 or more levels (group 3). The mean EPFI in group 1 was 1.5, with 48% having an EPFI of 1.5 or greater and 12% an EPFI of 2.0 or greater. The corresponding figures for group 2 were 1.5, 51% and 14%. For group 3, the figures were 1.7, 63% and 26%.

The effect of total pulmonary flow index (TPFI) on intercirculatory mixing also was analyzed. A direct correlation ($P < 0.001$) was found between EPFI and TPFI. Patients with a large TPFI and a single anatomic mixing site (ASD or VSD only) achieved better mixing than did those with a decreased TPFI and 2 sites available for mixing (ASD and VSD, and so forth). The data indicate that a large TPFI is conducive to achieving maximal mixing and that in children more than 1 year of age, poor mixing is more often due to decreased TPFI secondary to pulmonary stenosis or pulmonary vascular disease than to inadequate anatomic communications between the 2 circuits. Further analysis revealed a correlation ($P < 0.001$) between the TPFI and an index derived by dividing systemic arterial saturation by the hemoglobin concentration. Patients with TGA can be followed up with a periodic systemic arterial sample and the use of this index, thus in some cases avoiding repeated catheterization.

Objective Evaluation of the Effects of Direct Myocardial Revascularization on Ventricular Performance Utilizing Submaximal Ergometer Exercise Testing

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Thirty patients with severe obstructive coronary artery disease undergoing direct myocardial revascularization were studied at rest and with submaximal, supine bicycle ergometry at the time of coronary catheterization preoperatively, 6 weeks and 1 year postoperatively in an effort to evaluate the early and late effects of vein bypass surgery. Ventricular performance was assessed at rest and during exercise by measurement of cardiac index, heart rate response, oxygen consumption, mean systolic ejection rate and left ventricular end-diastolic pressure (LVEDP). External work load, pressure rate product and dp/dt were used to assess requirements for myocardial O_2 consumption, and ventricular performance curves were constructed.

Vein graft patency was associated with striking relief of angina even at greater postoperative stress levels, whereas graft closure was associated with persistence of angina or abnormal ventricular performance. Statistically, significant improvement in LVEDP and striking improvement in ventricular performance curves was evident in a group with good ventricular contraction as evaluated angiographically and with patent vein grafts. Less striking improvement could be demonstrated with moderate to severe impairment of ventricular contraction and patent grafts although angina was relieved. These benefits of vein bypass surgery were evident in the early postoperative study and persisted in the late study.

Reduction in Experimental Myocardial Infarct Size by Glucose-Insulin-Potassium Administration

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To study effects of glucose-insulin-potassium (GIK) on infarct size, epicardial electrocardiographic maps were taken in 12 sites 15 minutes after occlusion of the left

anterior descending coronary artery in 25 dogs. Twenty-four hours later creatine phosphokinase (CPK) activity and histologic changes were determined in transmural specimens from sites previously examined by electrocardiograms. In 10 controls (73 specimens) the inverse relation between epicardial S–T segment elevation (mv) 15 minutes after occlusion and myocardial CPK in international units/mg protein 24 hours later was highly significant (log CPK = −0.064S–T + 1.24, $r = -0.81$). In 13 dogs (113 specimens) GIK was infused for 24 hours starting 15 minutes after epicardial mapping. CPK depletion was less after GIK infusion at all levels of S–T segment elevation as demonstrated by a significantly lower slope −0.022ST ($P < 0.001$). For example, CPK in sites with S–T elevations of 3 to 6 mv, i.e., zones bordering infarcts and small infarcts, was always depressed in controls (6.7 ± 0.7) but was nearly normal in the GIK group (14.1 ± 0.7, $P < 0.001$). Histologic examination, as well as stains for glycogen and fat (14 dogs, 185 biopsy specimens), showed that in sites with S–T segment elevation after occlusion, early signs of necrosis did not occur in 36% of samples from the GIK group as compared to only 3% of the control group. Similarly, electron microscopy (4 dogs) did not show severe ichemia in 75% of specimens with S–T segment elevation in the GIK group compared with 8% in controls. Thus, histologic, histochemical, ultrastructural and enzymatic evidence indicates myocardial damage associated with the coronary occlusion was reduced by GIK.

Salvage of Myocardial Tissue by Coronary Artery Reperfusion Following Acute Coronary Occlusion

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It is generally considered that irreversible myocardial damage occurs after 60 minutes of coronary obstruction. The possibility that longer periods of ischemia might be tolerated was investigated by coronary reperfusion 3 hours after an acute occlusion. In 14 control dogs the anterior descending coronary artery was occluded for 24 hours, and in 6 the occlusion was released after 3 hours. Electrocardiograms were recorded from epicardial sites 15 minutes after occlusion, and myocardial creatine phosphokinase (CPK) activity was measured in transmural specimens from the same sites 24 hours later. In control dogs, S–T segment elevation (mv) predicted CPK (international units/mg protein): log CPK = −0.0611 S–T + 1.26 ($r = 0.79$, N = 102 sites). In the reperfused group the slope was −0.0113 S–T ($P < 0.001$), showing almost complete preservation of CPK activity at 24 hours. In 7 other dogs the acutely injured area was assessed from the zone of epicardial S–T segment elevation and the area of hypoperfusion using methylene blue injection. In control dogs allowed to survive 1 week, the anatomic infarct size at postmortem study 7 days later averaged 60% of that predicted from the acutely injured area. However, in reperfused hearts average infarct size at 1 week was only 10% of that predicted. In 4 dogs paradoxical movement of 7 pairs of intramyocardial beads studied cineradiographically was demonstrated 3 hours after coronary occlusion. Following reperfusion, the average difference between end-diastolic and end-systolic distance changed from −1.7 ± 0.7 mm to +4.9 ± 1.1 mm ($P < 0.01$), thus demonstrating the reversal of the abnormal wall motion. It is concluded that coronary reperfusion 3 hours after an acute occlusion prevents a substantial amount of myocardial necrosis.

Maximal Treadmill Exercise Electrocardiography: Correlations With Coronary Arteriography and Cardiac Hemodynamics

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Electrocardiograms were recorded during and at 2-minute intervals after maximal treadmill exercise in 100 patients and were correlated with coronary arteriograms, left ventricular (LV) cineangiograms, and resting and exercise cardiac hemodynamics. The incidence and extent of exercise-induced "ischemic" S–T segment depression increased significantly ($P < 0.01$) with increasing extent of coronary disease (CAD). A criterion of abnormality of 1.0 mm or greater S–T depression most accurately predicted the presence of CAD with a specificity (true negative) of 91% and a sensitivity (true positive) of 64%. Criteria of ≥0.75 mm and ≥0.5 mm S–T depression offered improved sensitivities (69% and 81%, respectively) but markedly reduced specificities (75% and 53%, respectively).

A significant correlation ($P < 0.01$) was found between increasing extent of exercise-induced S–T segment depression and the pulmonary wedge pressure during exercise. There were no correlations between the presence or extent of exercise-induced S–T depression and the resting or exercise pulmonary arterial pressure, cardiac index, stroke volume index, the resting LV dp/dt, LV end-diastolic pressure, exercise factor, LV ejection fraction, or presence of asynergy on the LV cineangiogram. The maximal treadmill exercise test provided a noninvasive method for predicting the presence and extent of significant CAD in the individual patient. Although a normal treadmill exercise test provided little insight into the underlying resting and exercise hemodynamics, 91% of patients with an abnormal treadmill test (≥1.0 mm S–T segment depression) had an associated increase in LV filling pressure with exercise.

Ectopic Rhythms Arising from Anterior and Posterior Fascicles of the Left Bundle Branch in Anterior and Posterior Myocardial Infarctions

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In the slow phase of sinus bradyarrhythmia occurring in acute myocardial infarction (AMI), an isorhythmic ventricular escape rhythm frequently emerges. In the majority of cases, QRS configuration does not favor idioventricular origin. Rather, the incomplete right bundle branch block (RBBB) with rsr′ in lead V_1, together with left or right axis deviation, suggest aberrancy. However, His bundle electrography in 11 such cases showed His spikes at or near the onset of the QRS, thus excluding aberrancy of junctional beats which should have normal His–Q intervals. The focus

was placed at a point equidistant between myocardium and His bundle, i.e., in the fascicles of the left bundle. From its fascicular point of origin, the impulse propagates peripherally, reaching first the respective territory of the left ventricle and then the other areas, thus the axis deviation. Simultaneously, the impulse travels centrally, reaching the main His bundle and thus the short His–Q interval, and finally descends along the right bundle to reach the myocardium of the right ventricle. All 4 anterosuperior fascicle foci occurred in patients with anterior infarction and all 7 posteroinferior foci in inferior wall infarctions. Without exception, these fascicular rhythms were benign and had disappeared by the twelfth day of infarction. We conclude that isorhythmic escape rhythms occurring in AMI frequently arise from a fascicle of the left bundle related to the infarction and indicate enhanced automaticity in that fascicle during the acute phase of ischemic injury.

Supernormality in the Human Heart

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This report documents 5 cases of supernormal (SN) conductivity, in the sense of unexpected normalization of the previously existing bundle branch block (BBB) and 3 cases of SN excitability in which impulses delivered to the ventricles propagated to the myocardium only in a circumscribed region corresponding temporally with the U waves of the preceding beat. In none of the cases could SN be abolished by atropine, thus suggesting absence of an important vagal role. In 3 cases of right BBB, spontaneous as well as electrically induced premature atrial beats were followed by normal QRS complexes only if they reached the right bundle during its SN phase. In 2 cases of bilateral BBB, strategically placed sinus P waves and induced atrial impulses were conducted with normal P–His and His–Q intervals. SN excitability was exemplified by 2 cases of fixed-rate pacemaker with failing batteries in which subthreshold impulses captured only in SN phase. The third case was one of acute myocardial infarction with a parasystolic focus in the inferior division of the left bundle, causing propagated beats only in the SN phase. SN conductivity in the atrioventricular (A–V) node was not found in an exhaustive search of His bundle electrograms of 45 patients with varying grades of A–V nodal block probably because the A–V node lacks phase 4 depolarization. We conclude that SN conductivity occurs in bundle branches and probably not in the A–V node. Its timing, response to atropine and observations made during His bundle electrography favor an electrophysiologic and not a mechanical-autonomic nervous system mechanism.

Hyperosmolal State Following Cardiac Arrest

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Among 764 patients observed in our Center for the Critically Ill, in whom measurements on serum osmolality were available, osmolality exceeded 350 mOsm/kg in 25 cases. All but 1 of these patients died. These observations confirm the lethal effects of hyperosmolal states previously reported by others.

Among the 25 patients, there were 6 in whom hyperosmolality followed cardiac arrest. Samples of arterial blood were obtained during the interval of resuscitation, and serum osmolality in these samples ranged from 351 to 403 mOsm/kg. Measurements before onset of cardiac arrest were available in 5 of these 6 cases, and in each instance serum osmolality had been between 270 and 320 mOsm/kg, a normal range. A 7.5% solution of sodium bicarbonate in amounts equivalent to between 132 and 265 mEq of sodium was administered during each resuscitation attempt, and in 5 of the 6 cases arterial blood pH was increased to more than 7.45. Striking increases in serum bicarbonate to a maximum of 79 mEq/liter and in arterial blood lactate up to 29.12 mM/liter were also observed. All of the patients died, 5 died within 1 hour and 1 died 4 days later.

These observations indicate that hyperosmolality, which itself is usually a fatal metabolic defect, appears as a complication of cardiac arrest or as a consequence of its treatment, or both. Until the mechanism of this hyperosmolal state is better defined, the present observations prompt us to use caution in employing large amounts of hypertonic solutions of alkalinizing drugs without concurrent measurements of blood pH and osmolality.

Defective Platelet Aggregation in Congenital Heart Disease

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Children with cyanotic congenital heart disease (CHD) and polycythemia may experience bruising, cerebral thromboses and excessive hemorrhage with surgery or even mild trauma. The platelet function of 70 children (aged 3 weeks to 17 years) with CHD was studied. In 15 of 37 children with cyanotic CHD and 4 of 32 with acyanotic CHD, platelet aggregation by adenosine diphosphate (ADP) (4 μM, 37°), noradrenalin (20 μM, 37°) and connective tissue was markedly impaired. Aggregation remained abnormal when these platelets were incubated with normal plasma. Plasma from these children did not impair the function of normal platelets in vitro. Electron microscopy studies and ADP content of functionally defective platelets were normal. Thirty-two percent of those with defective platelet aggregation had mildly prolonged Duke bleeding times and mild to moderate bleeding symptoms. Defective platelet aggregation was most frequently found in children under 10 years with moderate to severe cyanosis and hematocrit values above 50%. Common varieties of cyanotic CHD were approximately equally divided between normal children and those with defective platelets. Most children had been subjected to palliative, but not corrective, surgery and no excessive surgical bleeding was noted in any of the study group. Platelet factor 3, adhesion to connective tissue and clot retraction were normal. All children had normal platelet counts and coagulation studies. These findings reveal a platelet defect previously unrecognized in these children.

Diminution and Closure of Large Ventricular Septal Defects After Pulmonary Artery Banding

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The courses of 4 infants with large ventricular septal defect (VSD) and pulmonary arterial banding (PAB), followed by diminution or spontaneous closure of the VSD, seen at our center between 1960 and 1970 were reviewed.

The 4 babies on admission showed failure to thrive (below 3%), with recurrent respiratory infections and intractable congestive heart failure. There was marked cardiomegaly (cardiothoracic index-CTI 0.06–0176, average 0.67), increased pulmonary blood flow, and usually biventricular hypertrophy on the electrocardiogram. Initial catheterization performed between 2 and 11 months of age (average 5 months) showed a large left to right (L–R) shunt (Qp:Qs ratio 3.0–7.3:1, average 5.1:1) with elevated right ventricular (RV) pressure to at least 2/3 of systemic level. PAB was followed by remarkable clinical improvement, resolving cardiomegaly (CTI 0.47–0.53, average 0.50) and only RV conduction delay in all, except 1 child with RV hypertrophy, on the electrocardiogram. Repeat catheterization (ages 5 to 7 years) showed no L–R shunt in 2 children and only trivial shunting (Qp:Qs ratio 1.2:1 and 1.6:1) in 2 others. The RV pressure was half systemic in 3 children and was normal in 1. Left ventricular angiocardiogram showed no VSD in 1; in 3 others only a trivial stream of dye was seen, traversing the ventricular septum.

Spontaneous closure of a large VSD with congestive failure is relatively infrequent. Among our series of 40 infants having had PAB for VSD, the VSD diminished in size spontaneously in 4 children (10%). The contribution of the PAB to the closing of the large VSD will be discussed. Surgical reconstruction of the stenosed pulmonary artery (at the site of the band) will be required in the presence of an intact ventricular septum.

The Diagnosis of Aortic Atresia By Echocardiography

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The clinical diagnosis of aortic atresia and hypoplastic left ventricle is difficult in the critically ill neonate. Presently, accurate diagnosis depends upon cardiac catheterization and selective angiography, procedures which are associated with significant mortality in this age group. Since echocardiography is a noninvasive technique without risk, its application in the diagnosis of aortic atresia in the neonate seems ideal. Echocardiographic studies were performed in 11 neonates presenting with typical clinical signs of aortic atresia, absent to weak peripheral arterial pulses, massive hepatomegaly and gray color with shock-like appearance. The findings in 8 patients were strikingly similar. Their echograms revealed a large anterior ventricular cavity with an atrioventricular (A–V) valve (tricuspid) in the cavity. A ventricular septal echo was seen posterior to this valve and defined the anterior limits of a minute chamber. Occasionally, a distorted but recognizable A–V valve was recorded within the posterior chamber. A small aortic root echo was identified in only 2 infants. The diagnosis of aortic atresia and hypoplastic left heart was confirmed in all 8 patients at autopsy. The remaining 3 patients had normal echocardiograms. In light of this finding, cardiac catheterization was not performed. Correction of acidosis, hypoglycemia, hypoxemia and treatment of sepsis resulted in dramatic improvement in their clinical state, and subsequent cardiac evaluation was entirely normal in each instance. Echocardiography provides a noninvasive and accurate method of diagnosing aortic atresia in the neonate and thus precludes the use of cardiac catheterization.

Identification of Clinical Subsets in Cardiogenic Shock

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Data on 100 patients with cardiogenic shock (CGS) were reviewed in relation to clinical profile, hemodynamics (32 patients) and autopsy findings (71 patients). The study revealed that CGS is not a homogeneous entity and defined 3 clinical subsets. Subset 1 (56 patients) resembled experimental coronary occlusion and presented with rapidly developing shock, which occasionally followed an episode of hypotension (9 patients). Anterior infarction (56 patients) was invariable, and varieties of fascicular block (28 patients) were frequent. Radiologic pulmonary edema without significant cardiomegaly was characteristic. Autopsy revealed moderately increased heart weight (394 ± 17 g) and recent complete occlusion, subtotal obstruction or diffuse disease of the left coronary artery in all patients. In subset 2 (14 patients), CGS followed rupture or dysfunction of the mitral apparatus (11 patients), ventricular septum (1 patient) or free wall (3 patients). Classic physical signs were usually present, although a giant *v* wave in the pulmonary capillary wedge pressure tracing was the sole evidence of mitral regurgitation in 2 patients. CGS superimposed on heart failure characterized subset 3; 25 patients had earlier infarction and 20 failure before admission. Radiologic cardiomegaly was the rule. Grossly increased heart weights (564 ± 27 g) and evidence of previous infarction were seen at autopsy. Conceptually, infarction associated with sudden loss of contractility, a mechanically disadvantageous lesion and end stage failure characterizes subsets 1, 2 and 3, respectively, and CGS due to a critical loss of functioning myocardium results in all cases. However, patients in subsets 1 and 2 qualify as potential candidates for surgery. Since CGS is not a homogeneous entity and since the mortality with medical therapy exceeds 90%, early recognition of the clinical subsets may facilitate selection of patients for further investigation and possible surgery.

Dependence of Atrioventricular Junctional Automaticity on Sympathetic Tone

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Influence of sympathetic tone on automaticity of the atrioventricular junction (A–VJ) and sinus node (SN) was studied. Automaticity was evaluated in 10 dogs by

observation of escape rhythms after cessation of 5 minutes' drive at 240/min (overdrive). The SN escaped promptly after overdrive, and this rate was only slightly depressed by bilateral stellectomy. After overdrive in dogs with the SN crushed, the maximal cycle length of the A–VJ was 0.5 to 10.2 seconds (average 2.4 seconds), followed by stable junctional rhythm. After stellectomy automaticity of the A–VJ was depressed, with maximal post-overdrive cycle lengths of 2.4 to 21.4 seconds (average 9.1 seconds), slow erratic A–V junctional rhythm and ventricular escape complexes. After adrenalectomy and stellectomy the A–VJ was even more unreliable. In 3 reserpinized dogs automaticity of the A–VJ was also less reliable than that of the SN. In 10 other dogs the SN was arrested by physostigmine, 10 μg/ml infused into the SN artery. Propranolol, 10 to 100 μg/ml, was infused into the A–V nodal artery. Physostigmine alone resulted in A–V junctional rhythm at about 90/min. After beta blockade of the A–VJ, SN eserinization resulted in A–V junctional rates of 20 to 30/min and sometimes permanent asystole. Ventricular escape complexes were absent. Results confirm less reliable automaticity of the A–VJ compared to the SN and show greater dependence of the A–VJ on sympathetic tone for maintenance of rhythm. Hazard of sympatholytic drugs in persons with SN disease or A–V block is implied.

Comparative Hemodynamic Effects of Procainamide and Lidocaine in Patients With Acute Myocardial Infarction

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During acute myocardial infarction, procainamide may be utilized for suppression of ventricular ectopic rhythms refractory to lidocaine. Although procainamide is frequently successful in this capacity, its use in patients with myocardial infarction has been limited by concern for possible myocardial depression and hypotension. Therefore, the comparative hemodynamic effects of procainamide and lidocaine were assessed in 12 patients in the coronary care unit, 10 with AMI and 2 with left ventricular failure. Lidocaine, 100 mg was administered by intravenous bolus followed by an infusion of 2 mg/min for 20 minutes. Twenty to 30 minutes after cessation of lidocaine, procainamide, 100 mg in 3 minutes, was administered intravenously and followed by 2 mg/min for 20 minutes. Hemodynamic measurements were obtained before, 3 to 5 minutes after initial dose, and after 20 minutes of infusion. Lidocaine produced no significant ($P > 0.05$) changes from control: heart rate (HR) 84 beats/min, mean intra-arterial systemic blood pressure (BP) 82 mm Hg, pulmonary artery wedge pressure (PAW) 8 mm Hg, cardiac index (CI) 2.2 liters/min per m^2, peripheral vascular resistance (PVR 1,693 dynes sec cm^{-5}). Similarly, hemodynamics after procainamide were unaltered ($P > 0.05$) from control valves: HR 86/min, BP 84 mm Hg, PAW 9 mm Hg, CI 2.3 liters/min per m^2, PVR 1652 dynes sec cm^{-5}. No changes in P–R or QRS duration occurred after either drug.

These data indicate that procainamide, like lidocaine, in clinically effective antiarrhythmic doses resulted in no significant alteration of cardiac pump function in patients with AMI. Therefore, procainamide provides an effective and safe alternative to lidocaine in AMI when ventricular ectopic rhythms are refractory to lidocaine or the patient cannot tolerate lidocaine.

Determinants and Functional Significance of the Coronary Collateral Circulation in Patients With Coronary Artery Disease

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The significance of the coronary collateral circulation and the determinants of its functional development remain controversial. To evaluate these questions 104 patients with severe (>75% stenosis) coronary artery disease (CAD) documented by arteriography were studied. Seventy patients with collateral vessels were compared with 34 patients without collaterals. No significant differences ($P > 0.05$) in age, sex, prevalence of hypertension, abnormal glucose tolerance, lipoprotein abnormalities, smoking habits or family history of CAD were found among the groups as a whole or when compared for equal severity of coronary vessel involvement. However, the presence of collaterals correlated closely with extent of CAD: 46 patients with no CAD, 0% with collaterals; 1-vessel CAD, 42% ($P < 0.001$); 2-vessel CAD, 54% ($P < 0.001$); 3-vessel CAD, 81% ($P < 0.001$). To assess critically the functional significance of collaterals, 2 groups of 21 patients with subtotal or total occlusions of the left anterior descending artery were carefully matched for location and severity of stenoses in all vessels. All patients had collaterals, the groups differing only by the absence of collaterals to the left anterior descending artery in 1 group (NC) and their presence in the other group (C). For the following factors, there were no significant differences ($P > 0.05$) between the groups: New York Heart Association functional class III or IV, NC 50%, C 57%; anterior infarction, NC 27%, C 36%; positive Master test, NC 84%, C 69%; left ventricular end-diastolic pressure, NC 15, C 15 mm Hg; cardiac index, NC 2.8, C 2.5 liters/min per m^2; left ventricular dyssynergy, NC 52%, C 87%. It is concluded that the presence and extent of coronary collateral vessels are most closely related to the severity of CAD itself. In patients with similar degree of CAD, collaterals are associated with comparable clinical and functional status and confer no apparent additional benefit relative to patients without collaterals.

Usefulness of the Electrocardiogram in Assessment of Ventricular Performance and Comparison With Coronary Arteriography

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The relation between electrocardiographic (ECG) abnormalities and left ventricular function was evaluated in 104 consecutive patients with coronary artery disease (CAD), aged 26 to 65, undergoing cardiac catheterization and coronary arteriography. Data on 47 patients without pathologic 0.04 second Q waves (NoQ)

were compared to those of 13 patients with inferior infarction (IQ), 25 patients with anterior infarction (AQ) and 9 patients with anterior-inferior infarction (A-IQ). Results were left-ventricular end-diastolic pressure (LVEDP), NoQ 11, IQ 11, AQ 18 ($P < 0.001$), A–IQ 26 mm Hg ($P < 0.001$); cardiac index, NoQ 2.8, IQ 3.0, AQ 2.7, A–IQ 2.5 liters/min per m^2; left ventricular dyssynergy, NoQ 5%, IQ 31% ($P < 0.01$), AQ 68% ($P < 0.001$), A–IQ 78% ($P < 0.001$). Further analysis was undertaken of 43 patients with angiographically documented 3-vessel CAD ($\geq 75\%$ stenosis in all 3 major vessels), who differed only by the presence of Q waves in one group and their absence in the other. Data in 19 NoQ patients were compared to those in 8 IQ, 8 AQ and 8 A–IQ patients. Results were LVEDP, NoQ 11, IQ 10, AQ 17, A–IQ 26 mm Hg ($P < 0.01$); cardiac index, NoQ 2.7, IQ 3.0, AQ 2.5, A–IQ 2.6 liters/min per m^2; left ventricular dyssynergy, NoQ 0%, IQ 38% ($P < 0.01$), AQ 87% ($P < 0.001$), A–IQ 88% ($P < 0.001$). Thus ECG evidence alone of old AQ or A–IQ strongly suggests dyssynergy and elevated LVEDP, and allows more accurate prediction of left ventricular dysfunction than does coronary arteriography. In contrast, left ventricular performance may be normal even in the presence of 3-vessel CAD without Q or with inferior Q. It is concluded that specific QRS changes are closely associated with abnormal left ventricular segmental contraction and increased LVEDP in CAD.

Natural History of Severe Proximal Coronary Disease as Defined by Cineangiography (200 Patients, 7 Year Followup)

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Determining the survival rate in patients with severe proximal coronary lesions may help evaluate the efficacy of some present and future forms of surgical therapy. Mortality was reviewed in 200 patients with 80 to 100% occlusive lesions in the proximal coronary tree as defined by selective angiography. Patients with marked cardiomegaly, congestive heart failure or severe left ventricular impairment by left ventriculography were excluded, leaving only patients with normal or moderately impaired left ventricular function in the study. Eighty-four patients with 1-vessel, 82 with 2-, and 34 with 3-vessel involvement were followed up for 7 to 9 years. Single vessel anterior descending disease has a 4% yearly attrition rate or 30.5% 7 year mortality (11 of 36). Single right coronary or circumflex lesions demonstrated only a 1.8% yearly death rate or 12.5% in 7 years (6 of 48). Patients with 2- and 3-vessel disease had a 44% (36 of 82) and 70% (24 of 34) 7 year mortality rate, respectively. Survival in the group with anterior descending artery involvement was correlated with collateralization and anatomic location of the lesion. Of 10 patients with 100% occlusion of the anterior descending artery, 4 with faint or no collaterals died and 6 with excellent collateralization survived. Lesions above the first major septal perforator resulted in a 36% mortality (5 of 14): lesions below the perforator produced a 27% mortality (6 of 22). Survival is related to the number of vessels involved and single vessel anterior descending disease has a lower, but significant, yearly attrition rate. Collateral blood supply to the totally occluded anterior descending artery appears to increase survival.

Bundle of His Electrograms: "Fact of ArtiFACT"

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There are 3 criteria which help define whether or not one is truly recording electrical activity from the bundle of His, namely (1) anatomic location of the electrode(s), (2) configuration of the electrical complex, and (3) time of onset of depolarization within the P–R interval. When one uses the catheter technique to record bundle of His electrograms (BH) it is necessary to rely almost entirely on the time at which the suspected BH electrogram occurs. These studies demonstrate 4 methods to verify BH catheter recordings by (1) pacing the atrium at rapid rates, (2) introducing early premature atrial beats, (3) increasing vagal tone, and (4) driving through the BH catheter. The difficulty and methods of distinguishing BH electrograms from (a) atrial depolarization complexes, (b) atrial repolarization complexes, and (c) mechanical artifacts are demonstrated. Amplifier band pass filter settings and electrode configuration played the most prominent role in governing BH electrogram configuration. Filters with different roll-off characteristics (including log), band widths and center frequencies were compared with d-c-recorded BH electrograms. The ability to enhance artifacts or BH electrograms, or both, was demonstrated. The influence of bipolar electrode configurations demonstrated the variations in BH potentials caused by variations in (a) interelectrode distances, (b) recording area of the electrodes, (c) proximity to BH tissue, and (d) spatial orientation of bipolar electrodes. These studies emphasize the caution required to define accurately a BH electrogram recorded with a catheter electrode.

Effects of Propranolol and L-Norephinephrine in Acute Myocardial Infarction in Man

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L-norephinephrine (L–NE) and propranolol (Prop) could theoretically improve myocardial oxygenation in acute myocardial infarction (AMI) by either increasing oxygen delivery (L–NE) or decreasing O_2 demand (Prop). L–NE strikingly increased lactate utilization in 8 patients with myocardial infarction shock by increasing coronary perfusion pressure and blood flow. In contrast, the response to L–NE varied considerably in AMI without shock, for reasons probably related to more active coronary autoregulation of the noninfarcted myocardium. Since increasing perfusion pressure did not consistently improve myocardial O_2 availability in these patients, we evaluated the effect of Prop, an agent decreasing cardiac work and O_2 requirements. Prop (56 μg/kg per min) significantly decreased mean aortic pressure, time-tension index and probably contractility with little effect on heart rate in 10 patients with normal left atrial pressure and subnormal cardiac indexes. L–NE (0.113 μg/kg per min), in the same group, increased cardiac afterload. Prop appeared to decrease O_2 requirements since myocardial lactate and pyruvate extractions improved in face of decreased O_2 consumption and blood flow. Free fatty acids (FFA)

utilization varied. Increased myocardial O_2 demand by L-NE was met by a rise in myocardial blood flow as well as O_2 extraction. In the presence of normal myocardial metabolic findings L-NE caused a shift in substrate utilization. Extraction of lactate decreased; that of FFA strikingly increased. If myocardial metabolism was abnormal before drug administration, the response to L-NE varied. Whereas L-NE further decreased lactate, pyruvate and FFA utilization in most patients, myocardial metabolism markedly improved in others. This study suggests that in selected patients Prop may improve myocardial O_2 availability and be beneficial during AMI.

Is Coronary Sinus Monitoring in Acute Myocardial Infarction Useful? Studies in 25 Patients

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Prognosis after acute myocardial infarction is related to the oxygen availability and contractile state of the noninfarcted myocardium. Infarcted areas are poorly perfused in the acute state so that mixed coronary sinus (CS) blood is dominated by the metabolic state of the noninfarcted myocardium, suggesting that CS sampling might provide useful information regarding prognosis and efficacy of therapeutic interventions. We evaluated myocardial metabolism in 25 patients in the acute state of transmural infarction and related these findings to clinical and hemodynamic observations. Sequential metabolic measurements were made at 12 to 24 hour intervals for up to 72 hours in 20 patients. Coronary blood flow and myocardial O_2 consumption values (mean, range) were, respectively, 87 (57, 111) and 10.6 (5.7, 13.9) ml/100 g per min; extraction ratios for oxygen, lactate, pyruvate and free fatty acids were 68.9% (53, 82), 10.2% (−44, 38), 1.1% (−96, 38) and 12.6% (−20, 39), respectively. Eleven patients had lactate extraction ratios below 12% for at least 24 hours and were tentatively considered to exhibit "abnormal" myocardial metabolism. Most patients who changed from abnormal to normal metabolism demonstrated evidence of arrhythmias, left ventricular failure, or hypotension; in 2 or 4 patients who remained abnormal during 48 to 72 hours shock developed, and they died. All but 1 of the patients who had normal metabolism during the entire observation period did well. The following initial measurements were significantly different ($P < 0.05$) comparing abnormal to normal groups: pulse pressure −32 mm Hg; diastolic arterial pressure −23 mm Hg; mean arterial pressure −29 mm Hg; left ventricular work index −2.5 kg-m/min per m^2. Pulmonary arterial wedge pressure and arteriovenous O_2 difference were 5 mm Hg and 2.1 ml/100 ml higher in the abnormal group, but clear statistical significance was lacking. These observations suggest that CS monitoring in complicating infarction may be useful for prognosis and management.

Tritiated Digoxin Uptake by the Normal and Hypertrophied Rabbit Myocardium

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The relative importance of myocardial mass compared to serum levels of digoxin for achieving maximal concentration of digoxin is undetermined. Left ventricular hypertrophy (LVH) was induced in 6 rabbits by a technique of banding the aorta with the production of a significant gradient. The weight of the left ventricle of the banded rabbits exceeded that of the control animals by an average of 49.6% (2.39 or 4.81). These animals are compared with 5 control rabbits. Tritiated digoxin (125 μc/mg) in a dose of 0.045 mg/kg was given intravenously to each animal. Serum samples were collected every 15 minutes for 2 hours at which time the animals were sacrificed and all tissues analyzed for digoxin content by a method of chloroform extraction, column chromatography and liquid scintillation counting. There was no significant difference in serum levels between the control animals and those with LVH. A significant correlation ($r = 0.883$) was established between the serum concentration of digoxin and the total myocardial digoxin concentration. Serum concentration rather than myocardial mass is the determining factor in myocardial tissue concentration of tritiated digoxin; thus, the presence of cardiac hypertrophy does not undermine the usefulness of the serum level of digoxin.

The Mechanism of Activation of the Canine Endocardium

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To determine the mechanism of the sequence of activation of the intraventricular conducting system and subendocardial muscle, we studied isolated preparations of large areas of canine endocardium, using standard microelectrode techniques and surface recordings. It was possible to stimulate the bundle branches locally, without nonspecific activation of the underlying muscle, with either intracellular stimulation or surface stimulation close to threshold. The results show that the right bundle branch gives no impulse input to the septal muscle until after passing the base of the anterior papillary muscle, at which point fibers reflect back to the anterior and posterior septum to activate the muscle. The earliest point of *muscle* activation occurred at the apical free wall, with the right ventricular free wall endocardium, anterior papillary muscle, and the septum from apex to base following in sequence. The left bundle branch (LBB), its proximal major divisions, and the subendocardial Purkinje fiber network of the upper portions of the left ventricular cavity generally do not provide impulse input into ordinary ventricular muscle. Rather, the propagating impulse passes from the conducting system into muscle on the lower third of the septum, the ventricular apex, the bases of the papillary muscles, and the interpapillary free wall. Muscle depolarization then occurs from the apex to base of the ventricular cavity, and from base to apex on the papillary muscles. The divisions of the LBB of the canine heart meet on the high interpapillary free wall to complete a ring of tissue having functional continuity.

Second Degree Wenckebach Type Atrioventricular Block Due to Block Within the Atrium

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Two female patients 69 and 72 years old with a history

of paroxysmal supraventricular tachycardia were analyzed by His bundle and intraatrial recordings. The electrocardiogram showed sinus bradycardia (SB) in 1 patient and SB with sinoatrial Wenckebach in the other. The conduction times through the atrioventricular (A–V) node (A–H) and His-Purkinje system (H–V) were normal in both cases. The intraatrial (P–A) conduction time was slightly prolonged (55 msec) in 1 and normal (40 msec) in the other, during normal sinus rhythm. In both cases with atrial pacing from high right atrium (RA) the conduction time from the pacing impulse (PI) to atrial (A) activation in the area of the A–V junction (PI–A) progressively lengthened with increase in AP rate, and finally classic second degree Wenckebach type of block was manifested at cycle lengths of 460 and 465 msec. The PI to QRS interval (PI–R) showed a progressive increase before the blocked stimulus. The lengthening of the PI–R interval was due to progressive increase in the intraatrial (PI–A) conduction time. In the dropped beats the PI was not followed by an A wave and indicated type I block within the atrium. Similarly, during induced premature atrial beats the PI–A time progressively lengthened as the coupling interval was shortened. These findings were reproducible and were seen despite a 3-fold increase in stimulus strength and changes in electrode position along the lateral RA border. This study (1) demonstrates a hitherto undescribed site for the exhibition of second degree Wenckebach block, i.e., the atrium; (2) supports the existence of sinoatrial Wenckebach; and (3) suggests the atrium as another possible site for reentry and a cause for supraventricular tachycardia because of the degree of delay and block exhibited within the atrium.

A Study of the Effect of the Argus Computer System on Treatment Actions in a Coronary Care Unit

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A prospective study was made over a 2 month period to evaluate the influence of a dedicated computer system (ARGUS) on the mode of treatment of ventricular arrhythmias. Patients admitted to the Barnes Hospital coronary care unit were divided into 2 groups (A and B) of 20 patients each. Continuous monitoring by Argus was instituted on all patients as soon as possible and continued for an average of 32 hours per patient, resulting in a total of 1,278 hours of monitoring. Both groups were also monitored by conventional methods. Argus calculated the rate of premature ventricular contractions (PVC's) and detected the occurrence of certain premonitory combinations of PVC's in both groups but supplied these results to the nurses for group A only. The influence of Argus was studied by noting treatment actions consisting of an initiation or an increment in rapid-acting antiarrhythmic agents. In all, 33 actions were taken, 25 in group A and 8 in group B. For these patients, an average of 3.1 actions were taken for patients in group A but an average of only 1.3 for those in group B. Thus, computer monitoring resulted in a marked increase in treatment actions with rapid-acting antiarrhythmic agents.

Ten Year Experience With Isolated Starr-Edwards Mitral Valve Replacement

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Between April 29, 1961 and December 31, 1970, 1,081 Starr-Edwards (S–E) mitral valves were inserted in 1,073 patients at the Mayo Clinic. Of these, 604 patients (41% male and 59% female) underwent 608 operations for isolated S–E mitral valve replacement. The average age was 49 years, 97% were in New York Heart Association functional class III or IV preoperatively. Thirty-four percent of the patients had had previous cardiac surgery. Early mortality (within the first 30 days) after surgery was 15% (94/608). The most common cause of early mortality was low cardiac output, which accounted for 38% of the deaths. The incidence of early thromboembolic complications was 5%. Of the 510 patients who survived the first 30 days, followup study has been possible through April 1971 in 507 (99.4%) ranging from 1 month to 114 months (mean 44 months). Late mortality thus far has been 22%. Overall total mortality thus far is 35% (210/604). Of the entire group of 604 patients, 394 (65%) were alive in April 1971 with improved functional status. The most common cause of late death was chronic congestive heart failure in 29% (34/116) of the cases. Incidence of early thromboembolic complications following isolated mitral S–E replacement was 5% (31/608); the incidence of late embolic complications was 28% (145/510). At least 1 thromboembolic episode occurred in 28% (170/608) of the total group. Early mortality for isolated mitral valve replacement during 1961 through 1965 was 23% (51/225) and for 1966 through 1970 was 11% (43/383).

Syndrome of Ventricular Septal Defect With Aortic Insufficiency

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The course of 72 patients having ventricular septal defect (VSD) with aortic insufficiency (AI) followed up between 1950 and 1971 and involving over 600 patient years has been reviewed. The median age of onset of AI was 6.9 years (range 0.1–20.5) with male subjects comprising 61% (44/72). The median pulmonary to systemic flow ratio was 2.1 (range 1–5); moderate to severe AI was present in 61% (44/72); and significant pulmonary stenosis was present in 19% (12/72). The average duration of followup study prior to onset of AI was 2.9 years (range 0–15) with 3 patients experiencing AI 1.4 to 4.2 years after VSD closure. The average duration of followup after onset of AI and before operative in ervention was 4.3 years (range 0–18). Surgery was performed in 57% (41/72). During the followup period the condition of the patients deteriorated in 44% (32/72), improved in 6% (4/72) and did not change in the remainder. Whereas only 37% (27/72) were symptomatic at the onset of AI, congestive heart failure (CHF), dyspnea or fatigue subsequently developed in 57% (41/72). The overall mortality was

32% (23/72) with 16 intraoperative deaths, 6 from CHF and 1 unknown. Subacute bacterial endocarditis (SBE) occurred in 11% (9/72) and of these 7 required surgery, with 5 deaths. Impressive deterioration occurs in this defect especially when complicated by SBE or associated lesions.

Circulatory Responses to Graded Stimulation of the Carotid Chemoreceptors

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The role of the chemoreceptors in the control of circulation was studied in 13 anesthetized and artificially ventilated dogs. The carotid bifurcations were isolated and perfused at constant pressure, and the vagi were cut. Autologous blood, collected in a reservoir, was equilibrated at various pO_2 levels from 100 to 35 mm Hg, pCO_2 from 40 to 80 mm Hg and pH from 7.46 to 6.87, independently, and used to stimulate the chemoreceptors. Systemic arterial pO_2, pCO_2 and pH were kept normal. Reflex increases in aortic blood pressure and in hind limb perfusion pressure (constant flow perfusion) were first seen with pO_2 of 70 mm Hg and pCO_2 above 40 mm Hg. The vascular responses increased linearly with lower levels of pO_2 or higher levels of pCO_2, until respective tensions of 35 and 70 mm Hg were reached, which caused similar increases in blood pressure (88 and 81 mm Hg, respectively) and in hind limb perfusion pressure (76 and 68 mm Hg, respectively). Increasing the pH of the blood perfusing the chemoreceptors reduced these changes by more than 50%; decreases in pH, with normal pO_2 and pCO_2, caused marked vascular responses, indicating the important role of the pH in the activation of the chemoreflex mechanism. Thus, the chemoreceptors normally contribute little to circulatory control, but in hypoxia, hypercapnia or acidosis, they become a major regulatory mechanism, affecting mainly the peripheral vascular resistance.

Long-Term Observations in Patients With Angina and Normal Coronary Arteriograms

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Thirty-one patients (mean age 43.7 years) with angina pectoris (AP), myocardial abnormalities and normal coronary arteriograms were followed up. Nine patients had typical, and 22 atypical AP. Ten had abnormal serum lipids (6 type IV, 4 type II), 7 abnormal glucose tolerance test. An atrial sound in 6, and minimal cardiomegaly in 3 patients were noted. Nineteen patients had resting electrocardiographic (ECG) abnormalities (15 nonspecific S–T segment change, 2 left bundle branch block, 2 left axis deviation). Rest to exercise hemodynamics revealed increased left ventricular (LV) end-diastolic pressure in 21 patients (mean 11.2 ± 2.6 → 26.1 ± 6.1 mm Hg) ($P < 0.05$), while stroke work index increased (+12%). LV contractility assessed by Lv dp/dt/p (mean 1,340 ± 210 → 2710 ± 700 mm Hg/sec) and LV angiography was normal. LV ischemia was detected by abnormal lactate extraction with atrial pacing in 12 or >1 mm S–T segment depression during exercise in 15 patients.

After a mean followup period of 3.8 years, 26 patients managed with propranolol noted marked improvement of angina syndrome. No changes in hemodynamics or anatomy were noted in 5 patients restudied. Autopsy on 1 patient who died suddenly revealed normal coronary arteries and myocardium. In the remainder complications of ischemia, i.e., progression of symptoms, infarction and heart failure, were absent.

The fate of patients with AP and normal coronaries with LV abnormalities (ECG, metabolic or hemodynamic) appears favorable. The AP, usually atypical and frequently incapacitating, responds to propranolol. Long-term preliminary observations suggest a nonprogressive disorder.

The Relationship of Anginal Symptoms to Lung Mechanics During Myocardial Ischemia

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The syndrome of angina pectoris (AP) commonly includes sensations of chest tightness or difficulty in breathing. Since left ventricular (LV) dysfunction during myocardial ischemia incident with AP is well documented, secondary alterations in lung mechanics could relate to these symptoms. To examine the possibility of a pulmonary mechanical basis for AP we examined airway resistance (Raw) and lung volume (TGV) and compliance (C_L) in addition to LV hemodynamics during AP. Twenty-four AP patients with coronary heart disease confirmed by coronary arteriography but without bronchopulmonary disease or congestive heart failure were studied. LV hemodynamic and electrocardiographic responses were observed before, during and after relief of pacing-induced AP. C_L and body plethysmographic measurements of Raw and TGV were made under similar conditions. AP was associated with a sudden increase in LV end-diastolic pressure (EDP), mean +39%, $P < 0.01$, without change in LV end-diastolic volume (EDV), accompanied by a marked reduction in specific airway conductance (1/Raw/TGV), −38%, $P < 0.01$, at larger resting TGV (+21%, $P = 0.01$) and C_L declined (−27%, $P < 0.05$). LV diastolic compliance (EDV/EDP) decreased abruptly (−38%, $P < 0.01$). With relief of AP, these changes returned toward pre-angina values. Our data indicate that during periods of increased myocardial oxygen requirements, ischemia-induced LV dysfunction effects an abrupt increase in LVEDP. The resulting increase in pulmonary capillary pressure and congestion produces varying degrees of lung mechanical alteration consisting of increased Raw, hyperinflation and reduced C_L. The resulting change in ventilatory effort may be interpreted as chest tightness, heaviness or constriction by the patient with AP.

Hemodynamic Studies with a Permanently Implanted Left Ventricular Assist Device

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Hemodynamic effects of a dynamic aortic patch (DAP) for permanent ventricular assistance by diastolic aug-

mentation were studied in dogs. The DAP consists of an ellipsoidal silicone rubber pumping chamber. Dacron® velour backed with conductive polyurethane, which enhances the growth of a pseudointimal layer, lines the blood interface. The DAP is implanted into the wall of the descending thoracic aorta, and a pneumatic conduit is exteriorized through the chest wall to a drive unit. Nineteen experiments were performed in 10 anesthesized, open chest mongrel dogs immediately after implantation of the DAP. Hemodynamic indexes were measured with the patch inactive and during pumping. The following average changes from the unassisted (control) to the assisted condition were observed: tension-time index −23% (SD 10), left ventricular peak pressure −20% (SD 12), left ventricular stroke work −18% (SD 10), mean systolic ejection rate +36% (SD 11), cardiac output +16% (SD 8), aortic mean diastolic pressure +18% (SD 14), systemic vascular resistance −32% (SD 12) and mean coronary blood flow +41% (SD 27). Hemodynamic indexes in dogs with induced left ventricular failure exhibited greater percent changes.

In other studies evidence was obtained that the DAP causes minimal blood trauma and that the incidence of thromboembolization is negligible. These observations and the favorable hemodynamic response in the present study suggest the appropriateness of a limited clinical trial of the system in patients no longer responsive to medical management of chronic left ventricular failure.

The Unpredictability of the Response of Idiopathic Hypertrophic Subaortic Stenosis Patients to Oral Propranolol

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Thirty patients with idiopathic hypertrophic subaortic stenosis (IHSS) catheterized in our institution during a 3 year period were studied prospectively to correlate the long-term response to orally administered propranolol (Prop) with the response to intravenously administered Prop (0.15 mg/kg) at catheterization (Cath). Median followup period was 16 months. Before Cath 5 patients had New York Heart Association class I heart disease, 14 class II, 8 class III and 3 class IV. An elevation of peak basal gradient (>30 mm Hg) at Cath did not correlate with subsequent clinical deterioration. Two patients died suddenly, both with resting gradients of <20 mm Hg. Resting gradients of >15 mm Hg were abolished by Prop in 5 patients, but these patients had the same prognosis as the remainder. In only 5 of 29 patients did Prop abolish or substantially reduce the rise in peak gradient with a 20 mm Hg reproducible Valsalva; the percentage of patients in this group whose condition deteriorated was not reduced. Prop abolished the gradient increase (38 ± 8 mm Hg) after 0.4 mg of nitroglycerin (NTG) in 11 patients, but this was of no prognostic value. One positive correlation was that, exclusive of the 2 sudden deaths, the condition of 0 of 12 patients with a peak gradient of <50 mm Hg after Prop and NTG deteriorated vs. that of 3 of 8 of the remainder ($P < 0.025$).

These data further emphasize that sudden death in IHSS (presumably arrhythmic) occurs in the presence of minimal outflow tract obstruction. They suggest that the response to NTG before and after Prop may be an indicator of the long-term response to Prop, but indicate the difficulties in correlating long-term prognosis on Prop with Cath findings.

Serial Evaluation of Left Ventricular Volumes and Posterior Wall Movement in the Acute Phase of Myocardial Infarction Using Diagnostic Ultrasound

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Dimensional changes and posterior wall movement were followed serially in 10 patients in the acute phase of myocardial infarction (MI) using diagnostic ultrasound. Measurements included left ventricular (LV) internal dimensions in diastole and systole and LV posterior wall excursion and velocity (PWV). From these measurements, LV end-diastolic (LVEDV) and systolic volumes were calculated and changes in stroke index (SI) and cardiac index (CI) were followed. Five patients had anterior MI (Ant MI), 3 inferior (Inf MI), 1 apical MI and 1 combined anteroseptal-inferior MI. Averages of the serial measurements of LVEDV for each patient ranged from 57.52 ± 14.72 to 101.76 ± 17.43 cc/m², SI 27.83 ± 8.83 to 50.85 ± 6.94 cc/m², CI 2.70 ± 0.40 to 4.05 ± 0.42 liters/min per m², posterior wall excursion 0.97 ± 0.13 to 1.2 ± 0.07 cm and maximal PWV 4.08 ± 0.60 to 6.70 ± 1.00 cm/sec. Serial measurements in individual patients were variable during the acute phase of MI and demonstrated no trends in the 9 surviving hospitalization. In the 1 patient who did not survive hospitalization, depressions of SI, CI and PWV occurred before death. In 3 patients undergoing hemodynamic evaluation including dye-dilution CI determination, significant statistical correlation was noted with ultrasound CI determinations (no. = 6, $r = 0.998$). MI location was not associated with specific patterns or changes in LVEDV, SI or CI. Mean and maximal PWV were noted to be lower in patients with primary Inf MI (2.76 ± 0.30 cm/sec and 4.97 ± 0.64 cm/sec, respectively) than in patients with primary Ant MI (3.19 ± 0.48 cm/sec and 5.89 ± 0.80 cm/sec, respectively). The serial measurements obtained using ultrasound corresponded closely with the existing clinical circumstances and contributed to the description of the clinical status of the patient being monitored. The use of diagnostic ultrasound in the acute phase of MI permits noninvasive evaluation of serial changes in LV function defined by serial changes in LV volumes and PWV.

Maximum Rate of Pressure Decline in the Normal, Hypertrophied and Dilated Left Ventricle in Man

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The rate of ventricular pressure rise has received considerable attention in recent years, whereas the rate of pressure decline has been generally neglected. Maximal rate of pressure decline or negative dp/dt (Ndp) and of pressure rise or positive dp/dt (Pdp) were determined in 225 patients with a normal (NLV), pressure overload (PLLV) or volume overload (VLLV) left ven-

tricle. Mean Ndp for NLV (1,581 mm Hg/sec ± SE 41) was correlated ($P < 0.05$) with mean Pdp (1,858 ± 71) but significantly lower ($P < 0.001$). During isoproterenol infusion Ndp was unchanged (1,639 ± 134 to 1,715 ±112), whereas Pdp increased significantly (1,845 ± 183 to 3,957 ± 288, $P < 0.001$). Beta adrenergic blockade with oxprenolol caused a decrease in Pdp (2,041 ± 150 to 1,567 ± 87, $P < 0.001$) and no change in Ndp (1543 ± 79 to 1524 ± 47). In PLLV, Ndp was significantly higher (1,766 ± 68) and in VLLV significantly lower (1,344 ± 74) than in NLV (1,581 ± 41, $P < 0.05$), with a trend similar to that observed for Pdp. During positive inotropic stimulation, Ndp in PLLV did not change significantly (1,756 ± 118 to 1,986 ± 91) in contrast to Pdp, whereas it was increased in VLLV (1,339 ± 127 to 1,810 ± 145, $P < 0.01$).

The data indicate that the rate of isometric relaxation is different and can be independently altered from the rate of isometric contraction. The findings that ventricular hypertrophy and dilatation affect the rate of pressure decline and that chronic volume overload ventricles respond differently from normal and pressure overload ventricles to inotropic stimulation suggest that the study of isometric relaxation may be of importance in the evaluation of overall ventricular performance.

The Beneficial Effects of Nitroglycerin on the Degree of Myocardial Ischemia Occurring During Coronary Occlusion in the Conscious Dog

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It is generally believed that nitroglycerin (NTG) is contraindicated in acute myocardial infarction because of the potential deleterious effects of a decrease in coronary perfusion pressure and reflex increase in heart rate (HR). To define the effects of NTG during acute myocardial ischemia (MI), coronary occlusion was produced in 7 conscious dogs by 15-minute occlusions of the left anterior descending coronary artery (LAD) produced by inflating a balloon cuff previously implanted around the LAD. The degree of MI was estimated by summating the S–T elevation (Σ S–T) recorded from 12 myocardial electrodes. In 7 dogs MI was produced during control arterial pressure (AP) and HR and during intravenous NTG (100–200 μ/min) which produced an average decrease in mean AP of 14 mm Hg and increase in HR of 19 beats/min. After 15 minutes of control MI, Σ S–T averaged 85 mv. NTG resulted in an average *decrease* in Σ S–T of 13 mv ($P < 0.005$). To determine whether the beneficial effect of NTG was mediated by decreased afterload, AP was lowered by phlebotomy in 4 dogs so that systolic, diastolic and mean pressures were not different between occlusions during NTG and during hemorrhage. HR was held constant by atrial pacing. Σ S–T was less than control during NTG (−16 mv, $P < 0.01$) but greater during hemorrhage (+27 mv, $P < 0.005$). We conclude that in experimental acute coronary occlusion, NTG decreases the degree of ischemic injury, an effect not related to a decrease in afterload. Whether NTG dilates collateral vessels under these circumstances remains to be determined.

Anatomic Studies on Cloth-Covered Starr-Edwards Prosthetic Valves Implanted for Longer than Two Months

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Little anatomic data is available on the fate of cloth-covered struts of Starr-Edwards prostheses implanted for long periods. Of 27 prostheses implanted for 3 to 44 months (average 20) in 23 patients, 7 were recovered at reoperation and 16 at necropsy. Eighteen were aortic prostheses (14 model 2300, 4 model 2310), 8 were mitral (5 model 6300, 3 model 6310) and 1 tricuspid (model 2300). Each of the 27 prostheses showed some degree of tissue growth over the cloth of the struts and bases by histologic examination, although grossly some struts appeared free of tissue covering. The initial deposit appeared to be fibrin-platelet thrombi, usually at the apexes of the cages. This material organized into dense fibrous tissue containing fibroblasts, and, rarely, vascular channels and mononuclear cells. Electron microscopy (2 prostheses) showed that the organized tissue consisted of collagen fibrils with occasional fibroblasts. The amount of tissue growing over the struts was not proportional to the length of the implantation period, and it was not more extensive in mitral as compared to aortic prostheses or vice versa. Wear of cloth on the struts was observed in 2 of the 27 prostheses, both aortic, implanted for 16 and 25 months, respectively.

The Diffuse Nature of Coronary Arterial Atherosclerosis in Fatal Acute Myocardial Infarction

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Since the introduction of bypass grafts, knowledge of the distribution of coronary arterial atherosclerotic plaques has become essential. To determine the extent of atherosclerosis, the entire right, left anterior descending and left circumflex coronary arteries were examined histologically (3 six-micron thick sections per 0.5 segment) in 107 patients (aged 26–90 years [average 60]) with fatal acute myocardial infarction. Of the 3 major coronary arteries the average number per patient narrowed >75% by old atherosclerotic plaques was as follows: 2.4 in 74 patients with transmural necrosis, 2.1 in 9 patients with subendocardial necrosis and 2.4 in 24 patients who died suddenly (≤6 hours after onset of symptoms, no myocardial necrosis). Of the several thousand sections of coronary arteries examined in the 107 patients, only 4 sections were free of old plaques, and 3 of them had coronary emboli. Thus, coronary arterial atherosclerosis is a diffuse disease. The degree of luminal narrowing may vary, but some degree of atherosclerotic plaquing is present diffusely.

Papillary Muscle Necrosis in Active Valvular Infective Endocarditis

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Left ventricular papillary muscles (PM) were exam-

ined histologically in 41 patients (30 male, 11 female, aged 5 to 70 years [average 41]) who died of active infective (I) endocarditis (E). Necrosis was present in 1 or both left ventricular (LV) PM in 33 patients, diffuse in 6 and focal in 27. Of 17 anterior right ventricular papillary muscles examined, 8 had necrosis, diffuse in 2 and focal in 6. PM necrosis was not dependent on the site of vegetations: 12 of 14 patients with isolated aortic valve vegetations, 5 of 9 with isolated mitral valve vegetations, and 2 of 4 with isolated tricuspid valve vegetations had LV PM necrosis. Only 1 patient had significant narrowing of extramural coronary arteries, and in only 2 of 5 patients with emboli to intramural coronary arteries were emboli seen in involved PM. No patient with PM necrosis had necrosis of the free wall of LV beneath the PM. Valvular dysfunction with congestive cardiac failure occurred in 28 of 33 patients with and in 3 of the 8 patients without PM necrosis ($P = 0.015$). PM necrosis in active IE appears to be a consequence of congestive cardiac failure (CHF) rather than a cause of CHF in this condition.

Studies of Cardiac Pharmacology in Intact Animals and Isolated Cardiac Tissues

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A recently developed technique for perfusing isolated cardiac Purkinje fibers (PF) with blood of intact dogs (donor) permits simultaneous observation of drug-induced events in donors and PF's. Standard microelectrode techniques are used to study PF while donor arterial pressure and electrocardiogram (ECG) are monitored. Applicability of this system to the correlation of drug effects on PF transmembrane action potentials (AP) and donor was studied using intravenously administered procainamide (PA) and tritiated ouabain (O-^{3}H). At plasma PA concentration ([PA]) = 5–10 μg/ml (determined spectrophotometrically) AP amplitude, resting membrane potential and maximal slope of phase 0 decreased, AP duration and refractoriness increased; and conduction time along the PF and QRS duration in the donor ECG prolonged. Higher [PA] accentuated the changes, lower [PA] reversed them. For experiments on O-^{3}H, at various times after infusion, uptake in the isolated PF and PF excised from the donor were measured (as disintegrations/min per mg wet weight) and found equivalent when corrected for heart rate and stimulus cycle length. Onset of O-^{3}H induced ventricular arrhythmias on ECG occurred simultaneously with conduction disturbances in the PF. AP characteristics of PF removed from the donor at various time intervals after O-^{3}H or PA infusion were nearly identical to those of the isolated PF studied simultaneously. In all experiments, drug concentrations which changed PF AP and donor ECG characteristics were markedly lower than concentrations needed during Tyrode perfusion. These studies indicate that this blood perfusion technique provides an accurate means for correlating pharmacologic effects during electrophysiologic studies of donor animals and isolated PF.

Heart Size and Left Ventricular Function in the Year Following Myocardial Infarction

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The presence or absence of cardiomegaly is routinely used as an index of cardiac function. To assess the value of heart size in estimating postinfarction left ventricular (LV) function, 25 patients were evaluated 2 to 12 months after a transmural myocardial infarction by quantitative LV biplane angiography. Cardiac size was estimated by the cardiothoracic ratio (CTR) obtained from standard 6-foot posteroanterior roentgenograms and ranged from 0.35 to 0.68. LV end-diastolic volume (EDV) ranged from 67 to 331 ml/m^2 and ejection fraction (EF) from 0.09 to 0.64. Normal heart size (CTR <0.50) and relatively normal LV function (EF >0.50) were present in 6 patients; none demonstrated heart failure (paroxysmal nocturnal dyspnea or ventricular gallop, or both). Normal heart size was also present in 13 other patients, but each had a depressed EF (range 0.43–0.18, mean 0.35); 2 had heart failure. The remaining 6 patients demonstrated cardiomegaly, with EF ranging from 0.24 to 0.09; all had heart failure. The CTR is often thought to be an unreliable index of LV function because it does not accurately reflect LV size. Although CTR was useful in predicting LV size (i.e., EDV) ($r = 0.70$, $P < 0.002$), LV size did not accurately predict LV function (i.e., EF) ($r = 0.66$, $P < 0.005$). Furthermore, heart size predicted LV function ($r = -0.66$, $P < 0.005$) equally as well as did LV size ($r = -0.66$, $P < 0.005$). In conclusion, cardiomegaly was a reasonable indicator of postinfarction LV function, being associated with clinical heart failure and with EF <0.30. However, normal heart size was often associated with significant LV dysfunction (EF <0.45) that was not clinically apparent.

Abnormalities of Left Ventricular Contractility in Isolated Right Ventricular Overload

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Although it has been the traditional concept that left ventricular (LV) function is not affected by primary pressure or volume overload of the right ventricle (RVO), little information and no studies of LV muscle mechanics are available. Thus, 9 patients with primary RVO (atrial septal defect, 4; mitral stenosis, 2; pulmonic stenosis, cor pulmonale, pulmonary embolus) underwent evaluation of LV muscle function and hemodynamics during cardiac catheterization and were compared to 9 subjects with normal (N) hemodynamics and angiography. Both groups had normal LV end-diastolic pressures (N 8.7, RVO 8.1 mm Hg, NS), and ejection fractions (N 0.71, RVO 0.63, NS) (determined by single plane cineangiography). Instantaneous LV contractile element velocity (VCE) was calculated from developed isovolumic LV pressure (LVP) and its first derivative ([dp/dt]/[32·LVP]) and a pressure-velocity curve was constructed, from which maximal extrapolated VCE at zero LVP (Vmax) was determined. LV Vmax was considerably depressed in RVO (1.78) when

compared to N (3.10) ($P < 0.01$). These findings indicate that abnormalities of LV muscle function are associated with primary pressure and volume overloading of the RV despite normal LV hemodynamics. Such patients should not be considered suitable "normal controls."

The Relative Selection Sensitivities of Techniques to Evaluate Myocardial Function in Patients with Left Ventricular Hypertrophy

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Several indexes of left ventricular (LV) function separate patients with severe heart disease from normal subjects (N); however, their sensitivity in detecting minor abnormalities has not been evaluated. Thus, 9 N (cardiac index 4.10 liter/min per m^2, LV end-diastolic pressure 8.67 mm Hg) were compared with 21 patients with hypertrophic heart disease (HHD) (aortic stenosis, 14; hypertrophic cardiomyopathy, 7) (cardiac index 2.83 liters/min per m^2, LV end-diastolic pressure 16.1 mm Hg). Parameters of LV function evaluated were ejection fraction (EF) from single plane cineangiography, preejection period/LV ejection time (PEP/LVET), LVET/isovolumic contraction time (LVET/ICT), the first derivative of LV pressure at 50 mm Hg (dp/dt 50), and contractile element velocity (VCE) extrapolated to 0 load (Vmax) (VCE = [dp/dt]/[32·LV pressure]). Abnormalities in LV function could not be detected in HHD on the basis of EF (HHD 0.63, N 0.71, $P > 0.5$); PEP/LVET (HHD 0.356, N 0.342, $P > 0.5$); LVET/ICT (HHD 6.33, N 6.24, $P > 0.5$) but were readily evident by the analysis of Vmax (HHD 1.61, N 3.11 muscle lengths/sec, $P < 0.01$) and dp/dt 50 (HHD 1,422, N 1,852 mm Hg/sec, $P < 0.01$). These data indicate that indexes of muscle function (Vmax, dp/dt 50) are more sensitive indicators of minor abnormalities of LV dysfunction than indexes obtained principally from pump performance (EF, PEP/LVET, LVET/ICT).

Pharmacokinetics of Intramuscularly Administered Lidocaine

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Lidocaine is commonly administered intravenously for control of certain cardiac arrhythmias. Certain pharmacologic and practical advantages might be gained if it could be administered predictably by the intramuscular route as well. Ten patients free from arrhythmia or hepatic impairment (9 male, 1 female), aged 27–74 years (mean 52.6) were given 4 mg/kg body weight of 10% lidocaine HCl (Xylocaine®, Astra Pharmaceuticals) intramuscularly in order to study the kinetics of its absorption and elimination from the blood. This allowed comparison with similar curves described from intravenous studies where correlation with antiarrhythmic efficacy has been determined. Lidocaine is a known potent vasodilator, and absorption was uniformly rapid with a mean time to peak blood level of 13.5 minutes (range 5–30) and a mean peak blood concentration of 2.84 μg/ml (range 1.60–4.45). Elimination occurred exponentially at 2 successive rates: an initial, rapid rate with $t_{1/2} = 51$ minutes and a second, slower rate with $t_{1/2} = 132$ minutes. These elimination rates are virtually identical with those obtained after intravenous administration. Knowledge of these kinetic measures of lidocaine after intramuscular administration is essential in evaluating the place of this agent in the management of cardiac arrhythmias.

Comparative Mechanisms of Ventricular Dysfunction in Aortic and Mitral Stenosis Associated with Coronary Artery Disease

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The poor postoperative behavior of patients with aortic stenosis (AS) and mitral stenosis (MS) associated with significant obstructive coronary artery disease (CAD) suggested that important derangements of ventricular function could be ascribed to the influence of CAD. The following hemodynamics findings were present in 23 cases of pure AS and 31 cases of MS with greater than 50% obstruction of more than 1 coronary artery. Comparison was made with a similar number of patients with equally severe valvular disease and no coronary involvement (NCAD). In AS–CAD the cardiac index (CI), stroke index (SI), left ventricular systolic pressure (LVSP) and aortic gradient (AG) were significantly lower than in the AS–NCAD group (Table I). Similarly, in patients with MS–CAD, the CI, SI and right ventricular systolic pressure (RVSP) were reduced as compared to MS–NCAD (Table II). It is concluded that the common basic impairment in AS and MS is the inability of the involved ventricle to generate pressure proportional to the degree of valvular obstruction in the presence of significant CAD. Coronary pathology of only modest severity may be important when superimposed on overloading of the ventricles. Hence, selective coronary arteriography is suggested for all patients undergoing catheterization for valvular heart disease.

TABLE I

Patients with Aortic Stenosis

	AS–CAD	AS–NCAD
CI (liters/min per m^2)	2.16 ± 0.1	2.92 ± 1.6
SI (cc/m^2)	24.93 ± 3.61	37.10 ± 2.06
LVSP (mm Hg)	155.20 ± 9.64	202.88 ± 16.89
AG	38.3 ± 7.78	83.4 ± 12.1

TABLE II

Patients with Mitral Stenosis

	MS–CAD	MS–NCAD
CI (liters/min per m^2)	1.77 ± 0.21	2.44 ± 0.14
SI (cc/m^2)	21.14 ± 2.68	31.30 ± 1.90
RVSP (mm Hg)	39.33 ± 4.76	47.48 ± 5.03

Heritable Cardiac Conduction Disease: Left Axis Deviation, Right Bundle Branch Block, Complete Heart Block and Early Death

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Bundle branch disease and heart block have been ascribed to ischemic or degenerative processes. Recent experience with a patient with left axis deviation (LAD), right bundle branch block (RBBB) and intermittent complete heart block (CHB) suggested a familial conduction abnormality. Forty-five members of 5 generations were examined; 24 had abnormal electrocardiograms. Seven had LAD and RBBB; and 7 LAD, RBBB and intermittent CHB. Eight family members under 25 had lesser conduction defects: 2 had RBBB, 1 incomplete right bundle branch block (IRBBB), 3 LAD, and 2 combined LAD and IRBBB. Early death was a prominent feature; conduction defects, CHB and early death occurred in 10 affected persons. The genetic defect appears to be transmitted as an autosomal dominant with varying expressivity. This conduction abnormality, not recognized as a heritable disorder, raises serious questions about the ischemic or degenerative processes thought important in this disease. Further family and epidemiologic studies may yield valuable information about the etiologic factors and developmental changes leading to CHB.

Physiologic Effects of Intraaortic Balloon Pumping in Cardiogenic Shock

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Intraaortic balloon pumping (IABP) was used in 10 institutions under a common protocol to treat 81 patients with cardiogenic shock (CS) after acute myocardial infarction (AMI). In 73 patients refractory to conventional therapy (group I) initial mean heart rate (HR) was 108, arterial pressure 77/51 mm Hg, central venous pressure (CVP) 12 mm Hg, left ventricular end-diastolic pressure (LVEDP) 31 mm Hg, cardiac output 2.3 liters/min. Median times were shock onset 17 hours after infarction, initiation of IABP 5 hours after shock and total assistance 24 hours (range 2.5 hours–18 days). During IABP HR decreased 5%, systolic arterial pressure 9%, CVP 21% and LVEDP 45%, whereas diastolic arterial pressure increased 102% and urinary output increased from 14 to 51 ml/hour. Transmyocardial lactate metabolism improved in all 19 patients studied, averaging 9% production before and 12% extraction during IABP. Shock was reversed in 55 patients (75%). Improvement could not be maintained in 41 patients (56%) who died during or immediately after termination of IABP. IABP was successfully discontinued in 32 patients (44%) although 23 later died (median survival 48 hours, range 26 hours–45 days). Eight additional patients with CS had partial or transient improvement with medical treatment (group II). Shock was totally reversed with IABP in 7, and 3 survived. There were 10 complications of IABP including 1 death. IABP provides temporary clinical, hemodynamic and metabolic benefit in patients with CS after AMI and is valuable when short-term cardiac assistance is needed.

Late Systolic Mitral Regurgitation in Children

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The auscultatory complex of a midsystolic click or late systolic murmur, or both, in association with T wave inversion in the left ventricular surface leads of the electrocardiogram is sufficiently unique to clinically suspect mitral valve dysfunction with late systolic mitral regurgitation. In our clinic, we have followed up 43 children with clinical signs of late systolic mitral regurgitation. Their ages at the time of diagnosis ranged from 4 to 16 years. The longest period of followup has been 15 years. Selective left ventriculography in 8 patients demonstrated prolapse of the posterior mitral leaflet with various degrees of mitral incompetence in each instance. Intracavitary phonocardiography in 5 patients confirmed the intracardiac origin of the acoustic events recorded externally. Ultrasound studies in 10 patients confirmed posterior movement of the posterior mitral leaflet in late systole. Simultaneous phonocardiographic and echocardiographic studies demonstrated that the abnormal mitral valve motion coincides with the onset of the murmur in late systole. The frequency of this form of mitral dysfunction in children raises important questions regarding origin. Nine patients in our series have a definite history of rheumatic fever, and in 7 others it is highly suspect. We have not confirmed the presence of late systolic mitral regurgitation in an infant. These observations indicate that late systolic mitral regurgitation is prevalent in children and adds to the widening spectrum of this form of mitral valve dysfunction. Our studies further substantiate the usefulness of echocardiography in the detection of prolapse of the posterior mitral leaflet.

Saphenous Vein Bypass Surgery for Impending Myocardial Infarction

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Seventeen patients, all men 37 to 65 years old, were selected for surgery for impending myocardial infarction. All patients were admitted to the coronary care unit with recurrent and crescendo angina pectoris with electrocardiographic changes of acute ischemia without infarction. Intermittent ventricular tachycardia was present in 8 and ventricular fibrillation in 3 patients before operation. Coronary arteriography showed 3-vessel disease (at least 75% obstruction) in 12, 2-vessel disease in 2 and 1-vessel disease in 3 patients. Triple and double saphenous vein bypass shunts were performed in 14, a single shunt in 3 patients. Clinical, hemodynamic and radiographic follow-up data from 5 to 16 months are reported. Two patients failed to survive surgery. After operation, 3 experienced acute myocardial infarction within 6 months. Angina disappeared in all 15 living patients after operation, but reappeared infrequently in 3 patients 2 months postoperatively. Coronary arteriography and ventriculography performed 4 to 8 months after surgery showed

patency of the vein graft in all but 2 subjects. Ventricular contractility including areas of dyskinesia and akinesia were unchanged. Cardiac output and left ventricular pressure data were improved in 12 of the survivors.

Results of Aorta-Coronary Bypass Graft Surgery. Comparison with Arterial Implants and Medical Treatment

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Data on all patients in our institution treated with aortocoronary saphenous vein bypass grafts before July 1970 were reviewed. Combined operations (with implants, aneurysmectomies, valve replacement) were excluded. This left 67 patients with single or multiple (mean 2.3) grafts (group I). Review of all coronary arteriograms before advent of bypass graft surgery yielded 64 patients who would have been candidates for bypass grafts by the criteria used in selecting group I. Of these, 31 had received arterial implants (group II), and 33 were treated medically (group III). The following indexes were statistically analyzed in all groups: age, sex, functional classification, severity of obstructive disease, left ventricular ejection fraction and end-diastolic pressure, number of previous myocardial infarctions and electrocardiographic Q waves. No significant differences were found, except in functional classification (3.2 in group I, 2.6 in group III, $P < 0.05$). Mortality for the medically treated patients (group III) was 15.3% in 1 year, 24.2% total, mean followup period 28 months. Results in the surgical groups are shown in Table I. Total mortality at 1 year is not as yet significantly less in group I than in group III, due to the impact of operative deaths, but is significantly greater in group II. Bypass graft surgery resulted in significantly decreased late mortality and improved functional classification (3.2 to 1.5 postoperatively) compared to insignificant improvement in groups II and III.

TABLE I

Results After Surgery

Group	Followup (mean months)	Mortality (%)		
		Operative	Late	Total
I	14.6	10.5	1.5	11.9
II	28.0	19.4	16.6	36.0

Potentiation of Contraction by Premature Activation in Patients with Normal and Abnormal Left Ventricular Function

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It has been reported that in myocardiopathic rats the Bowdich effect is absent. This suggests a defect in electromechanical coupling. Accordingly, the enhanced cardiac performance that occurs in the contraction immediately following premature ventricular depolarization ventricular extrasystoles (ES), and in 3 with atrial fibrillation (AF). In 6 the left ventricle (LV), assessed by end-diastolic volume and pressure, ejection fraction and stroke volume, was normal (LVN): 7 had dysfunction (LVD). The following indexes were digitally computed from LV pressure (P) taped from catheter tip manometers: peak dp/dt, dp/dt over developed pressure (DP) at DP of 40 mm Hg $\frac{(dp/dt:DP = 40)}{DP}$, the highest value attained for the expression $\frac{dp/dt}{P}$ and Vmax (using P and linear extrapolation). Normal beats were compared with beats having a short preceding R–R interval (RR1) and long or normal R–R interval (RR2). Short RR1 was 436 ± 17 msec SEM for LVN and 458 ± 48 msec for LVD. The percent increase in contractility indexes for beats with short RR1 are shown in Table I.

TABLE I

Percent Increase in Contractility Indexes

Index	LVN	LVD
Peak dp/dt	25 ± 6	31 ± 4
$\frac{dp/dt:DP = 40}{DP}$	34 ± 6	37 ± 5
$\frac{dp/dt}{P}$	20 ± 5	29 ± 11
Vmax	39 ± 4	34 ± 8

Contractility increased in all beats in all patients when a normal or long RR2 followed a short RR1. This increase did not differ statistically between LVN and LVD or between short RR1 caused by ES or occurring in normally conducted beats in AF.

It is concluded that a deficiency in electromechanical coupling was not uncovered in these patients with LVD. Our study also demonstrated an alteration in inotropic state, representing an expression of the force-frequency relation in patients with atrial fibrillation.

Exercise Heart Rate and Blood Pressure in Electrocardiographic Stress Test Design

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We inquired whether the product of heart rate (HR) and systolic blood pressure (SBP) would permit a more precise definition of a "standard stress" than would the use of HR alone, measuring 223 tests on untrained patients over age 30 years and free of factors known to equivocate the "ischemic S–T depression" response. There were 89 negative and 134 positive responses. Mean age of the subjects was 49 years (range 30–72). In each test exercise was terminated upon evidence of exercise intolerance, S–T segment depression, or soon after reaching target heart rate. Peak exercise HR and HR × SBP were examined in relation to age and electrocardiographic response.

Patients with negative responses reached not less than 10 beats/min of target HR in 98% of tests. In patients with ischemic responses mean HR was much lower than in those with negative responses, but the

linear regression in the age range 40 to 68 years was evident (HR = 184 − 0.79 [age 40 years]), below which occurred 128 positive HR responses (98%). HR × SBP provided a wider dispersion of data than HR alone. A level was found (35 mm Hg/min) which would include 95% of those with positive responses, but <75% of those with negative responses reached even 30 mm Hg/min, so aiming for such a product would be pointless. In summary, the merit of HR × SBP for predicting onset of ischemia in the individual patient does not appear to hold for general application as a stress end-point in exercise testing, but 35 mm Hg/min may be used as an effective end-point for the occasional subject who achieves this level. However, there is an age regression of exercise HR that includes 98% of those with positive responses, the attainment of which is therefore a strongly negative result if no evidence of ischemia is manifested.

Noninvasive Determination of Infarct Size 5 Hours After Coronary Occlusion in the Conscious Dog

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This study was designed to predict infarct size (IS) within 5 hours in the conscious dog subjected to coronary occlusion and to measure changes in IS following isoproterenol administration. We have previously shown that IS is reflected by the pattern of serial serum creatine phosphokinase (CPK) changes during the 24 hours following occlusion. In the present study, serum CPK changes were measured in 21 conscious dogs subjected to coronary occlusion. Results were fit to a log normal function by least squares approximation. When the function was fit with values obtained during only the first 5 hours following occlusion, the derived curve predicted IS accurately (IS_p). Correlation coefficients between fit curves and actual serial 24 hour values in animals with occlusion alone were 0.94 ± 0.03 (mean ± SE), no. = 10. Differences between IS_p calculated from CPK changes during only the first 300 minutes and infarct size (range: 0.4 = 60 g) based on myocardial CPK analysis were small, 0.3 ± 2.4 g (mean ± SE). In 11 additional dogs isoproterenol, 0.015 mg/kg subcutaneously, was administered at least 10 hours after coronary occlusion. In all, subsequent serum CPK values deviated from those predicted by the log normal function. Hence, IS calculated from 24 hour serum CPK changes exceeded IS_p by an average of 219% ($P < 0.01$). Extension of infarction produced by isoproterenol was corroborated by postmortem myocardial CPK analysis. Thus, anticipated serum CPK changes, IS and quantification of extension can be determined promptly and noninvasively by appropriate analysis of early serum CPK elevations in individual conscious dogs.

The Effect of Variation in Arterial Oxygen Tension on Fetal Circulation

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The cardiovascular effect of changes in fetal arterial oxygen tension (pO_2) was studied in 7 closed-chest fetal lambs maintained in normal physiologic condition connected to an extracorporeal circuit functioning as an "artificial placenta." While fetal rectal temperature was maintained at 37 to 39C, umbilical arterial (UA) pH 7.30 to 7.40, UA pCO_2 35 to 45 mm Hg and placental flow (extracorporeal) 110 to 130 ml/kg per min, fetal circulation was investigated by dye-dilution technique at UA pO_2 of 20 to 30 mm Hg (fetal normoxia) and 35 to 45 mm Hg (fetal hyperoxia). Dye was injected successively into superior vena cava (SVC), inferior vena cava, right ventricle (RV) and left ventricle (LV) while being sampled from the ascending and descending aorta (DA).

During fetal normoxia, effective cardiac output was 305 ± 28 ml/kg per min, LV output 153 ± 25 ml/kg per min, pulmonary circulation time 5.8 ± 0.8 seconds and a large right to left (R–L) ductal shunt was present in each instance. SVC flow was directed to the right ventricle and through the ductus arteriosus into the descending aorta. During fetal hyperoxia LV output increased markedly to 269 ± 26 ml/kg per min, approximating the effective cardiac output, pulmonary circulation time decreased to 2.1 ± 0.3 seconds, whereas R–L ductal flow disappeared in 5 and markedly decreased in 2 instances. From this study it appears that, in fetal lambs, hyperoxia beyond an UA pO_2 of 35 mm Hg leads to closure of ductus arteriosus and marked decrease in pulmonary vascular resistance while allowing a sizable shunt through the foramen ovale.

A Method of Quantifying the Need for Surgical Therapy in Clinical Myocardial Infarction Shock

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Determining the need for mechanical support or acute revascularization, or both, before irreversible myocardial damage occurs presents a major problem in the treatment of myocardial infarction (MI) shock. By describing the magnitude and the shape of the central indicator-dilution curve using a mathematic model which quantifies the dye curve by 4 independent indexes, flow, and the delay, dispersion (non-mixing) and mixing mean transit times, more than 1,000 indicator curves from 197 patients with septic, nonseptic, and myocardial infarction shock, and from preoperative control patients without shock were analyzed. Mixing time (t_m) reflects changes in the durational aspects of myocardial contractility. Dispersive time (t_d) ordinarily reflects transit across pulmonary small vessels, but some patients with MI have a large cardiac nonmixing volume which appears related to the size of the infarct and its penumbra of ischemic myocardium. The persistence of a t_m >7.5 seconds and presence of a cardiac nonmixing volume with a t_d of >7.5 are signs of medically refractory MI shock requiring circulatory support. Of 28 patients with MI shock none survived in whom both t_d and t_m values were not decreased below 7.5 seconds by medical or mechanical support therapy. Intraaortic double balloon counterpulsation was used in 9 MI patients. The 3 patients resuscitated from acute MI shock all had reductions in t_d and t_m. The 6 nonsurviving patients did not. With these indexes it appears possible to quantify the effectiveness

of medical therapy and the need for mechanical cardiac assistance, and to identify those MI patients in whom acute myocardial revascularization offers the only chance for survival.

Electrophysiological Correlates of Aberrancy in Diseased Hearts

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Conduction disturbances, including aberrancy (Ab), seems to be more common in diseased than in normal hearts. The causes of increased aberrancy are uncertain. Electrophysiologic study of diseased human heart muscle provides clues in this regard. Transmembrane potentials were recorded from specimens of human papillary muscle with attached Purkinje fibers, and left ventricular free wall. Records were obtained during stimulation at cycle lengths of 200 to 2,000 msec and during spontaneous beating. Diastolic potential was reduced (−45 to −75 mv) due to low resting potential or diastolic depolarization of automatic cells. Amplitude and maximal rate of rise (Vmax) of action potentials (AP) initiated in such cells were low. V̇max of AP from left ventricular muscle was less than predicted, suggesting reduced responsiveness. Occurrence of similar changes in appropriate portions of the bundle-branch system (BBS) would predispose to increased Ab in diseased hearts, as would prolongation of the terminal phases of repolarization, which was commonly seen. Finally, findings that very early nonpropagated premature responses sometimes resulted in a striking decrease in the V̇max of the postextrasystolic beat suggest that concealed reentry within the BBS could be an additional factor underlying increased Ab.

Experimental Left Ventricular Akinesis

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Experimental myocardial infarction resulting in chronic left ventricular akinesis was created using a 2-stage ligation and agar injection of branches of the left coronary artery in 8 mongrel dogs. The effects of atrial pacing, increased afterload and beta blockade on left ventricular (LV) hemodynamics were studied 8 weeks after infarction. Atrial pacing from 120 to 180 beats/min caused a striking decrease in LV end-diastolic pressure (EDP) from 40 ± 3 to 14 ± 3 mm Hg. In the paced state LV end-diastolic volume measured cineangiographically decreased, whereas cardiac output and mean aortic pressure were unchanged. Beta blockade at a fixed paced rate increased LV failure with a rise in LVEDP of 6 mm Hg and a 20% decrease in cardiac output. Angiotensin induced increases in afterload at fixed paced rates resulted in similar deterioration in LV function with a 12 mm Hg increase in LVEDP over resting levels. These studies suggest that (1) the postinfarction chronically akinetic LV is dependent upon catecholamine support, and (2) pacing at high rates in the presence of chronic LV akinesis strikingly improves LV function.

Changes in Left Ventricular Wall Movement Following Exercise, Atrial Pacing and Acute Myocardial Infarction Measured by Reflected Ultrasound

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Movement of the posterior wall of the left ventricle was assessed using an ultrasound technique in a variety of clinical circumstances. Maximal posterior wall velocity (PWV) was measured as the maximal slope of the wall movement from the end-diastolic position to the end-systolic position, and posterior wall excursion (PWE) was measured as the maximal amplitude of movement anteriorly. In 11 normal subjects maximal PWV increased from a mean of 37 mm/sec at rest to 96 mm/sec after maximal erect exercise ($P < 0.001$), and PWE increased from 4.0 mm at rest to 6.8 mm after exercise ($P < 0.001$). The effect of heart rate (HR) alone on posterior wall movement was evaluated in 6 patients using the technique of atrial pacing. Increasing the HR resulted in a reduction in both maximal PWV and PWE. At identical HR in 5 patients there was a significant increase in both PWV and PWE during exercise compared to atrial pacing. In 8 patients with documented acute anterior myocardial infarction maximal PWV decreased by 26% and PWE decreased by 46% during the first 36 hours after infarction. In the 2 patients in whom it was measured an increase in pulmonary arterial pressure was associated with a reduction in both PWV and PWE and as the pulmonary arterial pressure returned toward normal, the posterior wall motion also improved. It is suggested that this method provides a noninvasive bedside assessment of left ventricular function following acute myocardial infarction independent of HR.

Left Ventricular Function and Coronary Anatomy Before and After Myocardial Infarction

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Complete clinical, hemodynamic and angiographic studies were performed in 5 patients before and from 2 to 22 months after myocardial infarction. Four had anteroseptal infarctions and 1 an inferior infarction. In all cases there was significant progression of coronary artery disease which correlated with the electrocardiographic area of infarction and the site of left ventricular contraction abnormality. Deterioration in contraction pattern, end-diastolic and end-systolic ventricular volumes (EDV, ESV), stroke work (SW) and systolic ejection fraction (SEF) were pronounced in 4 of 5 patients (Table I). The study provided a unique opportunity to compare left ventricular function before and after infarction by quantitative angiographic methods. The data confirm our previous impression that angiographic methods are sensitive to changes in left ventricular function associated with coronary ar-

TABLE I

Data in 5 Cases

Index	Case no. 1	2	3	4	5
LVEDP (mm Hg)					
Pre	12	8	14	...	10
Post	25	12	6	14	5
EDV (cc/m²)					
Pre	79	83	71	75	66
Post	123	88	62	120	68
SV (cc/m²)					
Pre	44	44	35	51	39
Post	26	38	33	37	29
SEF (%)					
Pre	51	53	49	67	59
Post	21	43	53	31	42
SW (g-m/m²)					
Pre	57	66	63	...	53
Post	24	59	64	55	42

tery disease. Correlation is demonstrated among progression of coronary arterial obstruction, local contraction abnormalities in the area of coronary occlusion, and deterioration in myocardial pump performance.

Systolic Intervals in Children with Normal and Diseased Hearts

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The ejection and preejection components of the total electromechanical systole have been measured from simultaneously recorded electrocardiogram, heart sounds and central arterial pulse, and have been shown by other workers to be of value in assessment of left ventricular performance in adults. In this report, this method was extended to children with normal and diseased hearts. The interval from the onset of QRS to the aortic component of the second sound (QS_2) was taken as the total systole. The left ventricular ejection time (ET) was measured on a carotid or axillary pulse record. The preejection period (PEP) was computed as the difference between the 2 periods. In 50 resting normal children, 3 to 20 years of age, PEP was 65 ± 13 msec (mean ± SD) and ET was 277 ± 23 msec. Since ET is heart rate-dependent, it was normalized using the regression equation: Ejection time index (ETI) = ET + 1.3 HR. ETI in the normal children was 386 ± 12 msec. PEP correlated weakly with age, weight (Cath $P < 0.05$), height ($P < 0.005$) and diastolic blood pressure ($P < 0.05$), but it had no significant correlation with the heart rate. PEP and ETI were measured in patients with various heart diseases. Prolonged PEP and reduced ETI coincided with a clinical impression of left ventricular dysfunction. In a small number of children who underwent cardiac catheterization, PEP showed significant correlation with the peak dp/dt ($r = 0.75$, $P < 0.005$) and the ejection fraction ($r = -0.95$, $P < 0.0005$).

Ionic Basis of Low Resting Potential in Diseased Human Heart

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Specimens of atria from patients having chronic atrial disease (CAD) are characterized by the presence of large numbers of fibers with low levels of resting potential (E_r) (−40 to −60 mv), a condition which predisposes to conduction defects and reentry. Delineation of the ionic basis of the low E_r could provide clues to the mechanisms responsible for arrhythmia in such patients. Low E_r could result from: (1) reduced intracellular potassium concentration [$(K^+)i$]; (2) reduced permeability of the cell membrane to K^+ (P_{K^+}); (3) increased permeability of the cell membrane to sodium (P_{Na^+}); (4) other causes. E_r of isolated, perfused specimens of the right atrial appendage (RAA) was measured using standard glass microelectrode methods during exposure to graded levels of (K^+) in both 150 and 0 mM Na^+ Tyrode solution. The results show that E_r is not altered by variation of (K^+) between 1.8 and 16 mM in either 150 or 0 mM Na^+ Tyrode solution; that 0 mv was obtained when Tyrode (K^+) was 160 mM. These findings suggest low E_r is not due to either reduced $(K^+)_i$ or increased P_{Na^+} but more probably is due to reduced P_{K^+}. The insensitivity of E_r to variation of (K^+) between 1.8 and 16 mM suggests that the conduction abnormalities associated with low levels of E_r in patients with chronic atrial disease will not be influenced by serum K^+ levels. These findings also suggest that 1 approach to raising the level of E_r and improving conduction in patients with CAD would be to increase the rate of electrogenic transport of Na^+ across the cell membrane rather than attempt to influence the passive effects of K^+ and Na^+ on E_r.

Nitrous Oxide as an Analgesic in Acute Myocardial Infarction

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Use of nitrous oxide (N_2O) as an analgesic in acute myocardial infarction (AMI) was evaluated in a coronary care unit. A double-blind study compared N_2O (a mixture of 36% N_2O and 64% oxygen) with O_2 (100%). Fifty-two episodes of myocardial infarction pain were studied in 40 patients. Gases were administered by face mask for 5 minutes each, the sequence being random. N_2O-O_2 was given first in 27 episodes; it decreased pain in 13 and abolished it in 7. O_2 was given first in 25 episodes; it decreased pain in 8; with subsequent N_2O, pain was decreased in 3 and abolished in 10. Drowsiness was produced in most patients. Side effects were light headedness in 3, necessitating cessation of gas inhalation in 1 patient. There were no significant changes in cardiac rhythm, pulse rate or blood pressure. Unlike the narcotic agents, N_2O does not induce gastrointestinal upsets or vagotonia. Evaluation in an additional 56 episodes of pain in 53 patients defines a role for N_2O as an effective analgesic agent and sedative for mild to moderate pain, and as an adjunct

to standard analgesic agents in severe, especially recurrent, pain associated with AMI.

Sudden Unexpected Death From Coronary Heart Disease: Relationship of Specific Risk Factors and Pathologic Findings

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As part of a 25 year study of ischemic heart disease in residents of Rochester, Minnesota, the medical records and the hearts obtained at autopsy of those who died suddenly and unexpectedly from coronary heart disease (CHD) were reviewed. Of 286 autopsy cases (83% of all such deaths), no risk factors were present in 95. In the remaining 191 cases, 73 patients had obesity and 50 had hypertension as their only risk factor. Severe coronary arterial narrowing existed in all but was more diffuse in those with hypertension. Coronary thrombi were found in 26% of obese patients, 20% of those with no risk factor, and 12% of those with hypertension. Of the coronary thrombi, 95% were acute in obese patients, but only 29% were acute in hypertensive patients. Demonstrable myocardial lesions (acute or old) were found in 78% of hypertensive patients, 60% of obese patients and 52% of those with no risk factor. The myocardial lesions were transmural in 38% of hypertensive patients, 20% of those with no risk factor, and 7% of obese patients. Myocardial rupture occurred in 18% of patients with hypertension, 4% of those with no risk factor and 1% of obese patients. In sudden unexpected death from CHD, the presence of prior risk factors was associated with severe morphologic cardiac damage. Hypertension was the most significant of the risk factors considered.

Factors Influencing Flow Through Aortocoronary Artery Saphenous Vein Bypass Grafts

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Flow through over 200 saphenous vein bypass grafts has been evaluated interoperatively by electromagnetic flowmeter and postoperatively by angiography. Although pressure and resistance determine flow, specific factors operate in direct myocardial revascularization procedures to influence these basic principles. Assessment of the peripheral coronary bed with regard to adequacy of outflow tract and extent of disease and collateral circulation is important. Flow through 1 vein graft was influenced by placing a second vein graft to another major vessel supplying the same vascular bed. Flow competition between the vein graft and the coronary artery (CA) itself may contribute to the occlusion of either the graft or the diseased CA. Intraoperative vein graft flows to the right CA ranged from 50 to 135 cc/min, in the left anterior descending CA from 50 to 250 cc/min, and circumflex CA from 50 to 180 cc/min. Retrograde flow in the CA is of importance in certain situations. Reflux from the CA into the vein graft, occasionally into the aorta, can be explained by absence of valves in the vein segment and the differential pressure and resistance between the intramyocardial system and the aorta. Operative technique, angle of insertion of the vein into the CA, size disproportion between vein and CA, and the number of vein limbs from a single aortic anastomosis and linking of the graft influence flow. Traumatic factors during vein preparation may damage intima and contribute to intimal changes that lead to reduction of blood flow. Postcardiotomy syndrome and the attending inflammatory processes reduce and often obliterate blood flow in the vein graft. Definition and consideration of these factors is of critical importance in improving patency rate and providing better clinical results.

Pseudo Type II Atrioventricular Block

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Electrophysiologic studies using His bundle recordings have demonstrated that in type II (Mobitz) second degree atrioventricular (A–V) block, the level of block is within the ventricular specialized conducting system (VSCS). Four patients aged 15 to 56 years with no history of spontaneous A–V block were studied using atrial pacing and His bundle recordings. In each patient atrial pacing at a given cycle length resulted at times in 2:1 A–V block in which the nonconducted atrial impulses were blocked in the VSCS (pseudo type II) and at other times in 1:1 A–V conduction. This apparent discrepancy was resolved when the effective refractory periods (ERP) of the A–V conducting system were determined using the extra stimulus method.

After the eighth sinus beat (A_1) a premature atrial depolarization (A_2) was introduced at progressively shorter intervals. The shortest H_1–H_2 at which H_2 conducts to the ventricles determined the ERP of the VSCS. In each patient the ERP was longer than that of the A–V node. This fact combined with an analysis of the initiation of the stimulation sequence explained the apparent discrepancy. When the first atrial capture beat during atrial pacing at a rapid rate resulted in an H_1–H_2 interval which was less than the determined ERP of the VSCS, a pseudo type II A–V block occurred. When the H_1–H_2 interval of the first atrial capture was greater than the ERP of VSCS, 1:1 conduction occurred. The frequent use of atrial pacing and His bundle recordings makes recognition of pseudo type II A–V block important because of the therapeutic implications.

Mechanism of Cardiac Failure in Experimental Patent Ductus Arteriosus

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Left ventricular (LV) failure and subendocardial (Endo) fibrosis may occur in patients with patent ductus arteriosus and unobstructed coronary arteries. We tested the hypothesis that this occurs because Endo blood supply becomes inadequate to meet myocardial oxygen needs. Variable aortopulmonary shunts were made in 10 dogs, and shunt flow, systemic flow and

coronary flow (CBF) were measured with electromagnetic flowmeters. Subendocardial and subepicardial (Epi) flow were measured with radioactive microspheres. Since LV Endo flow is diastolic, it was estimated from a diastolic pressure-time index (DPTI) calculated from the area between the superimposed aortic and LV pressure curves. LV myocardial oxygen needs were estimated from the tension-time index (TTI).

Shunts ranging from 500 to 2,500 cc/minute were well tolerated when CBF was greater than 65% in diastole and the LV was homogeneously perfused (Endo: Epi 1:1). Although total CBF increased proportional to TTI in all experiments, systemic flow decreased and LV end-diastolic pressure increased significantly ($P < 0.01$) when diastolic CBF fell below 65% and subendocardial muscle became relatively underperfused (Endo: Epi <0.7:1, $P < 0.01$). These changes in myocardial performance were not related to the absolute shunt flow but to its effect on diastolic pressure time relations and myocardial oxygen requirements. Relative underperfusion of LV subendocardium occurred when the ratio DPTI/TTI (supply/demand) fell below 0.8 ($P < 0.01$). We conclude that cardiac failure associated with patent ductus arteriosus occurs when Endo blood flow is sufficiently altered to make this flow inadequate to meet myocardial oxygen needs. These changes are predictable from pressure measurements alone.

Incidence and Nature of Arrhythmias in the Early Hospital Post-Coronary Care Unit Phase of Acute Myocardial Infarction

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Although the intensive coronary care unit (CCU) has made possible recognition of occult and potentially life-threatening arrhythmias in the immediate period following acute myocardial infarction (AMI), systematic investigation of the prevalence and types of serious arrhythmias in the early post-CCU hospital period is lacking. Accordingly, in 42 patients with AMI, analysis of arrhythmias was undertaken in the CCU (2–8 days) and on the medical ward during the second week of hospitalization after discharge from the CCU. During the latter period, continuous, taped 10 to 12 hour electrocardiographic (ECG) monitoring was carried out utilizing a portable ECG recorder (PECG). In the CCU, 36 patients (85.7%) had arrhythmias: ventricular ectopic beats (PVC's), 30 patients (71.4%), of whom 5 had ventricular (V) tachycardia (T) and 2 had V fibrillation; atrial ectopic beats (PAC's), 8 patients (19.0%); junctional (J) rhythm, 11 patients (26.2%); advanced or complete atrioventricular block, 5 patients (11.9%). Two weeks post-AMI, PECG revealed arrhythmias in 31 patients (73.8%); PVC, 27 patients (64.3%) of whom 2 had short runs of VT, 2 had V bigeminy, and 1 had paired PVC's; PAC's, 10 patients (23.8%); J rhythm, 3 patients (7.1%). Among the 5 who had no arrhythmias in the CCU, PECG revealed arrhythmias in all consisting of PVC's (3), VT (1), J rhythm (2) and PAC's (1). Late arrhythmias disclosed by PECG could not be predicted from rhythm disturbances in the CCU. In contrast to continuous PECG surveillance, clinical and routine ECG recording during the post-CCU period revealed arrhythmias in only 10 patients (23.8%). Thus, during the early post-CCU period following AMI, as in the CCU, serious cardiac arrhythmias occur frequently and may be undetected by routine methods. These data indicate the need for more intensive arrhythmia monitoring in patients with AMI during the intermediate hospital period after discharge from the CCU.

Massive Acute Pulmonary Embolism—Deceivingly Nonspecific Manifestations

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Patients with massive acute pulmonary embolism have few signs and symptoms traditionally described for pulmonary thromboembolic disease. Thus, dependence on evidence of pulmonary infarction often results in failure to identify such patients. Ninety of 160 patients in the Urokinase Pulmonary Embolism Trial had massive pulmonary embolism, demonstrated by pulmonary angiography to obstruct at least 2 lobar pulmonary arteries.

Dyspnea was present in 80% of these 90 patients, apprehension in 61%, and palpitations in 14%. Chest discomfort occurred in 80%, but was pleuritic in only 52%. Hemoptysis occurred in 27%. Most patients had a well defined predisposing condition: recent surgery or immobilization, congestive heart failure, malignancy, or use of oral contraceptives. Tachypnea and tachycardia were common, 88% and 63%. Increased pulmonic component of the second sound was present in 61%, rales 51%, third or fourth heart sound 47%, pleural rub 17%, clinical shock 14% and pericardial rub 1%. Twenty-two patients had only 1 of these findings, and 13 patients had none. Fifty-eight percent of patients had no phlebitis on admission. Fifteen percent of patients had a normal chest X-ray film. The arterial blood pO_2 was below 70 mm Hg in 56 patients, 71 to 90 mm Hg in 13, and above 90 mm Hg in 1 patient. Electrocardiographic RST segment and T wave changes occurred in 52% and 42% of patients, respectively, but traditional electrocardiographic manifestations of acute cor pulmonale were present in only 31%. The clinical diagnosis of pulmonary embolism, often massive, must be considered in any predisposed patient with sudden unexplained dyspnea.

Surgical Management of Acute Evolving Myocardial Infarction: A Coronary Circulatory, Metabolic and Angiographic Profile

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Coronary revascularization was applied as the principal therapy in 15 patients with acute myocardial infarction. All patients were operated on while acute electrocardiographic evolution of myocardial infarction was in process. In each case, chest pain persisted beyond 48 hours; however, overt shock and intractable heart failure were not evident. Thirteen of the 15 survived surgery following an average of 2.5 aortocoronary anastomoses per case. Coronary arteriography,

left ventriculography, coronary blood flow, myocardial lactate extraction, and coronary sinus: arterial creatine phosphokinase (CPK) gradients were studied immediately before surgery. Coronary arteriography demonstrated 3-vessel obstruction (>50%) in 11 of 15. Coronary blood flow, using a constant antipyrine infusion method, showed abnormally low values, averaging 78 cc/100 g per min ± 21 (normal 92–120). Myocardial lactate production was observed in 13 of 15. Lactate production occurred at rest in 3 and during controlled tachycardia (100–120/min) in 10. A coronary sinus: arterial CPK gradient was observed in all cases. Two to 7 days after surgery, restudy showed coronary blood flow to increase from 78 to 135 cc/100 g per min (P <0.01). Myocardial lactate extraction was normal in all cases (mean 28.9%) despite controlled tachycardia at 140/min. Clinical observations (2 weeks–7 months) in the 13 survivors showed these patients to be free of coronary pain, arrhythmia or heart failure. This study suggests that early surgical intervention with coronary revascularization, when myocardial infarction is clinically progressive, may be effective in reducing mortality and morbidity by limiting the extent of infarction.

Indirect Assessment of Coronary Artery Bypass Grafts

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Fifty-seven patients (mean age 50 ± 1.4 SE) were studied before and after coronary artery bypass graft surgery (CABG) utilizing indirect techniques. Fifty had at least 1 myocardial infarction preoperatively. Phonocardiograms, carotid arterial tracings, apex cardiograms and electrocardiograms were obtained preoperatively in all and 2 weeks after CABG (49) and 2 to 4 months after CABG (32). Cardiac catheterization and angiographic studies demonstrated significant (>70% narrowing) 3-vessel coronary artery disease (CAD) in 13, 2-vessel CAD in 35 and 1-vessel CAD in 9. There was generalized reduction in left ventricular (LV) contractility in 8 and marked reduction in 1 or more localized areas in 36. Only 1 patient preoperatively had significant mitral regurgitation (MR).

Fourth heart sounds (S4's) were present preoperatively in 56, 2 weeks after CABG in 47 of 49 studied (no significant difference, NS), and 2 to 4 months after CABG in 31 of 32 studied (NS). Third heart sounds (S3's) were present in 30 preoperatively, in 30 of 49 2 weeks post-CABG (NS), and in 20 of 32 at 2–4 months (NS). In 9 new S3's developed 2 weeks after CABG but in 9 the pre-CABG S3's disappeared. Before CABG, 10 had systolic murmurs compatible with but not specific for MR, 2 had paradoxically split second heart sounds (S2's) at rest, and 37 had early systolic sounds suggesting early clicks or split first heart sounds. There was no significant change in the incidence of systolic murmurs, splitting of S2's or early systolic sounds after CABG.

These studies demonstrate the following: (1) CABG's do not in the relatively early postoperative period completely reverse areas of reduced LV compliance which are responsible for the genesis of S4's; (2) the influence of CABG is more variable regarding presence or absence of S3's, but a few patients acquire new S3's in the early post-BABG period; and (3) early systolic sounds are relatively common in patients with CAD, whereas paradoxical splitting of S2's are uncommon at rest. Neither changed significantly after CABG.

Protective Zone for Ventricular Fibrillation

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The ventricular vulnerable period (VP) is a 20 to 40 msec interval during ventricular repolarization when a 0.5 to 1.0 watt sec discharge (S_1) can precipitate ventricular fibrillation (VF). Termination of VF even if attempted within seconds requires large energies (50–100 watt sec). We have observed that VF produced by S_1 is prevented if a second 0.5–1.0 watt sec pulse (S_2), is coupled to S_1. To be effective, S_2 must be delivered within a critical interval of time following S_1, which we define as the protective zone (PZ). S_2 is ineffective in preventing VF if delivered before or after the PZ. This PZ has been observed in each of 30 mongrel dogs with both transthoracic (underdamped capacitor) and endocardial (right ventricular unipolar square wave) discharges. The PZ begins 10 to 40 msec after the end of the VP and has a duration of 25 to 90 msec. The duration of the PZ varies inversely with heart rate (60 to 300 beats/min). For a given heart rate, the time of onset of the PZ (inner boundary) is fixed in the cardiac cycle and is independent of the location of S_1 in the VP. In contrast, the outer boundary of the PZ maintains a constant relation to S_1. It is suggested that the PZ reflects the disparity in the duration of repolarization of the ventricular myocardium and the specialized conducting system.

Effects of Conditioning on Plasma Catecholamine Levels During Exercise in Patients with Coronary Artery Disease

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As an index of adrenergic activity during exercise (Ex), arterial plasma catecholamine (Cat) levels were measured before and after a program of physical conditioning (Cond). All 7 patients studied had a positive Ex test, and either angina or a remote myocardial infarction. They were tested on a bicycle ergometer to angina or fatigue, and then trained on the bicycle for 10 to 18 weeks, 3 to 5 days/week. Cat levels were determined by a double-isotope derivative method. A Cond effect, with increased predicted max VO_2 ($PMVO_2$), was seen in 5. During Ex at 400 to 700 kpm/min, heart rate (HR) decreased from 147.3 ± 6.5 to 126.7 ± 6.4 P <0.001, whereas Cat decreased from 1.60 ± 0.27 to 0.73 ± 0.07 μg/liter, P <0.01. The 2 patients who did not undergo Cond did not manifest decreased HR, or increased $PMVO_2$, and Cat levels were slightly higher after training. At peak achieved work load, Cond patients had decreased HR and Cat after Cond; patients without Cond showed slight increases of each after training. These responses were significantly different, P <0.02. However, all pa-

tients increased their peak load even if no Cond effect was seen. The data suggest that Cond decreased sympathetic activity during Ex, but this observation seems unrelated to effort tolerance.

Prevention of Primary Ventricular Fibrillation in Acute Myocardial Infarction

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The prevention of primary ventricular fibrillation (PVF) is the single most important function of the coronary care unit. This study documents the prevention of PVF in 771 consecutive cases of acute myocardial infarction. In the initial 139 cases (group I) no prophylactic intravenously administered lidocaine or procainamide was used. The incidence of PVF in these patients was 6% (9 of 139). The average time interval from onset of symptoms until hospital admission in this group was 9.2 hours. Intravenously administered lidocaine was begun prophylactically at this point (group II, 632 cases), and treatment was initiated using the usual criteria of: (1) 5 premature ventricular beats (PVB's)/min; (2) R on T; (3) bursts; and (4) multifocal PVB's. The prophylactic treatment was then modified to begin with 1 PVB, and now all patients with suspected myocardial infarction (last 217 cases) receive a 75 mg bolus of lidocaine followed by a 2 mg/min drip infusion for 24 hours. If the PVB's are not effectively prevented by a 5 mg/min lidocaine drip then 100 mg of procainamide is given intravenously over 3 minutes followed by a continuous drip of 2 to 6 mg/min. The average time interval from onset to hospitalization in group II was 7.1 hours. Twenty-nine percent were hospitalized within 1 hour; 59 percent within 4 hours. The incidence of PVF in these 632 patients receiving prophylactic intravenous therapy was 0.2% (1 in 632). PVF was therefore reduced from 6% (9 of 139) to 0.2% (1 in 632) by use of prophylactic intravenously administered lidocaine or procainamide.

Structural Alterations in Tissue Cardiac Valves Implanted in Humans and Cows

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Sixteen tissue valves implanted 7 to 240 days (mean 87) were examined at necropsy in 8 human beings (H) and in 7 cows (C): fresh autogenous pericardium in 1 H and 3 C; fresh autogenous fascia in 1 C; glutaraldehyde-fixed human fascia lata in 2 C; formalin-fixed porcine aortic valves in 3 H; and glutaraldehyde-fixed porcine aortic valves in 5 H and 1 C. Gross and histologic examination of the glutaraldehyde-fixed porcine aortic valves disclosed that their structure was well preserved and showed no foci of necrosis. The sinus surfaces of these cusps were covered by 1 or 2 layers of mesothelial-like cells which in turn were covered by thin layers of fibrin. The cusps were not significantly thickened, and each was freely mobile. In contrast, the cusps of each of the other 4 types of tissue valves were focally necrotic, contained small calcific deposits, were thickened by either fibrin deposits or fibrous tissue, or both, and had decreased mobility; 2 valves had superimposed large thrombi. Thus, glutaraldehyde-fixed porcine aortic valves were well preserved structurally. In contrast, formalin-fixed heterografts lost their cellular structure after similar periods, and fresh autogenous tissues thickened and retracted.

The Association of Vascular Ring and Unusual Facial Appearance

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This report is concerned with the unique syndrome of the association of vascular ring and unusual facial appearance. From 1964 through 1970, 11 patients with vascular ring between the ages of 7 days and 9 months were seen. Seven of these 11 patients demonstrated significant mental retardation. Among these seven mentally retarded infants, 4 had unusual facial appearance and low-set ears. Coloboma, facial paresis and choanal stenosis were revealed in 3 of these 4 infants. Three symptomatic infants underwent surgery to release the vascular compression. However, 2 died with respiratory failure after surgery in spite of the release from vascular ring. Our experience suggests that choanal stenosis and retaining oral secretions due to mental retardation may play an important role in the respiratory problem of these cases. Since the surgical outcome of the vascular ring would not necessarily be favorable when associated with those abnormalities, the surgical indications should be carefully considered. Cayler (1967) demonstrated the association of facial paresis and intracardiac abnormalities as the facio-cardiac syndrome. However, no mention was made of the association with vascular ring. The high incidence of unusual facial appearance with vascular ring in our cases would suggest that facio-vascular ring syndrome is a developmental abnormality.

Exercise-Induced Ventricular Irritability: Hemodynamic and Angiographic Correlations

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Exercise-induced ventricular irritability (EIVI) may be of value in identifying patients at risk of sudden death. Thirty-two patients experienced EIVI during submaximal exercise testing. EIVI was always transient and was manifest as ventricular tachycardia (5), bigeminy (2), coupled ectopic beats (8), multiple ectopic beats (6), and accelerated ventricular rhythm (1). Pacing tachycardia induced ventricular irritability in only 1 of 18 tests in this group.

Coronary atherosclerosis (CAS) was present in 23 of the 32 patients (72%). Eighteen of these 23 experienced ischemic electrocardiographic changes with exercise. Coronary arteriography revealed diffuse disease, with only 1 patient having single vessel involvement. Each of the 3 major arteries was graded 0 (no disease) to 5 (total obstruction), and the average summed arteriographic score was 10.3. Collateral circulation was present in 74% and ventricular asynergy in 70%. Average ejection fraction (EF) was 55% and average left ventricular end-diastolic pressure (LVEDP) was 12 mm Hg.

These data were compared with observations in a group of patients who did not experience EIVI but were similar with respect to age and the presence of CAS. There was a significantly higher incidence of

multiple vessel disease in patients with EIVI (96% vs. 70%, $P = 0.02$). Differences in mean arteriographic score, EF, LVEDP, presence of collaterals and asynergy were not significant. Thus transient ventricular irritability induced by exercise in patients with CAS is indicative of severe double or triple vessel obstructive coronary disease.

Beat to Beat Alterations in Contractile State as the Mechanism of Spontaneous Pulsus Alternans in Man

ROBERT F. ZELIS, MD, FACC*; ROBERT J. CAPONE, MD; EZRA A. AMSTERDAM, MD, FACC; DEAN T. MASON, MD, FACC, Davis, California

Although pulsus alternans is well recognized as a manifestation of severe myocardial disease it is not clear whether this results from beat to beat variations in left ventricular (LV) filling pressure or LV inotropic state. Thus, in 4 patients with spontaneous pulsus alternans secondary to severe aortic stenosis or cardiomyopathy, at the time of diagnostic left heart catheterization, high-fidelity LV pressure (LVP) and its first derivative (dp/dt) were measured. Pressure-velocity curves were constructed from which contractile element velocity (VCE) at 0 LVP (Vmax) was determined. (VCE = dp/dt/32·developed LVP.) The peak LVP of the high beats (H) was 192.3 mm Hg compared to 179.4 for the low beats (L) ($P < 0.01$). LV end-diastolic pressure was 32.0 mm Hg for H and 32.2 ($P > 0.5$) for L, suggesting that the Frank-Starling mechanism cannot explain the variable peak LVP. Rather, the finding that Vmax was 1.06 for H and 0.99 for L ($P < 0.05$) suggests that a beat to beat variation in inotropic state independent of the preceding R–R interval (H 606.7 msec, L 607.5 msec, $P > 0.5$) is responsible for the alternating peak systolic left ventricular pressure in pulsus alternans in man.

Summation and Voltage Dependency in Rabbit A–V Nodal Fibers

DOUGLAS P. ZIPES, MD*; CARLOS MENDEZ, MD; GORDON K. MOE, MD, PhD, Utica, New York

This study demonstrates summation in the rabbit A–V node (A–VN) and dependency of the nodal action potential rise time (dv/dt) on the resting membrane potential. We produced summation in 2 ways. First, we divided the atrium and the floor of the coronary sinus to establish 2 noncontiguous, anatomically separate atrial inputs to the A–VN. Conduction to His occurred when both sides of the atrium were stimulated together at premature cycle lengths which produced local responses in the N region when stimulating either side singly. Second, with the atrium undivided, we stimulated the atrium and His bundle together, at intervals which allowed the simultaneous arrival of the advancing wavefronts at the impaled N cell. This collision resulted in an N action potential which occurred slightly earlier and had an increased dv/dt and amplitude, suggesting that nodal cells, as other cardiac cells, are voltage-dependent. Further evidence was provided by the influence of the N region on nodal action potential contours according to the direction of propagation. During orthograde conduction, cells close to N in the AN region have a larger dv/dt and cells in the NH region have a smaller dv/dt, than these same cells have during retrograde conduction. Since dv/dt affects conduction velocity, faster conduction occurs in the proximal portion and slower conduction in the distal portion of the A–VN during orthograde conduction, while the reverse happens during retrograde conduction. This balance accounts for similar total A/VN orthograde and retrograde conduction times in the rabbit.

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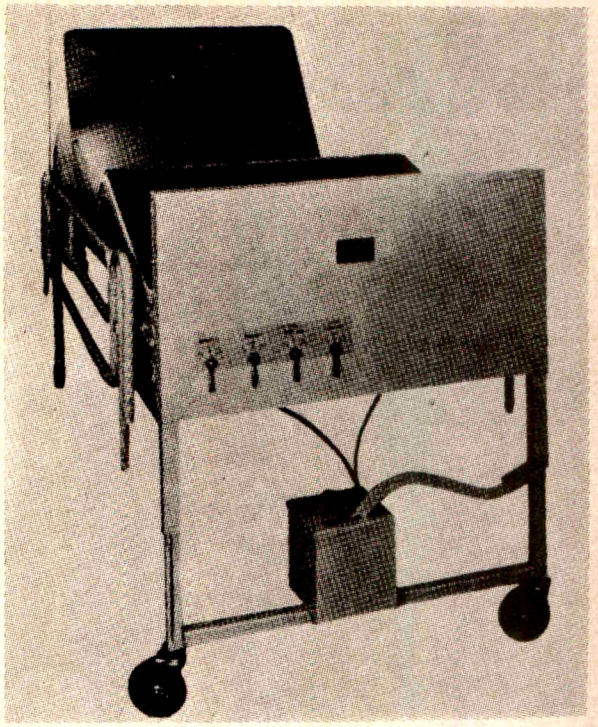

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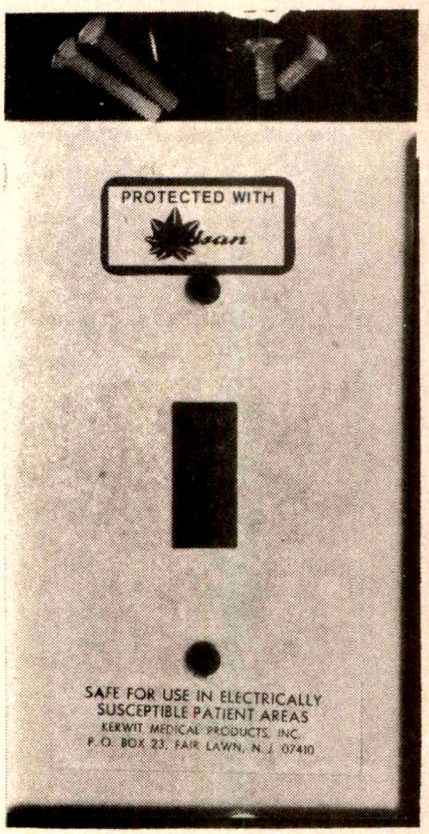

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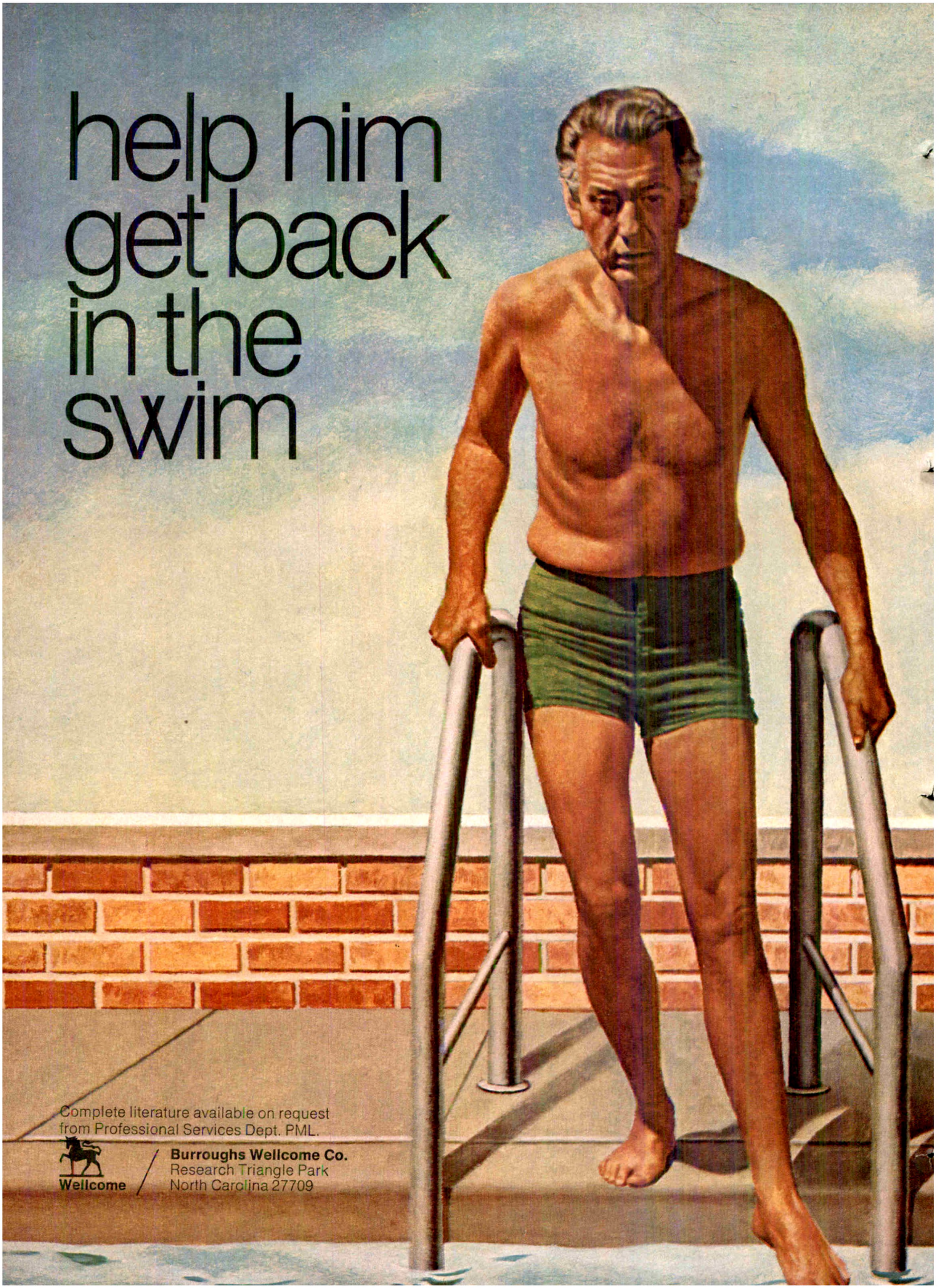
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Your anginal patient wants to return to near-normal exercise tolerance. A reassuring therapeutic regimen can help.

In the pharmacologic management of angina pectoris, the straight C-chain molecule has clearly proven its value. Most particularly in nitroglycerin.

Cardilate (erythrityl tetranitrate), an effective coronary vasodilator, is not simply another nitrite. It is the nitrite that most closely resembles the chemical makeup of nitroglycerin.

For this reason, Cardilate can offer *all* of these advantages:

- improves exercise tolerance
- relieves anginal pain
- reduces nitroglycerin intake
- has longer therapeutic effect than nitroglycerin (*up to 4 hours*)

NITROGLYCERIN	CARDILATE
$H_2-C-O-NO_2$ $H-C-O-NO_2$ $H_2-C-O-NO_2$	$H_2-C-O-NO_2$ $H-C-O-NO_2$ $H-C-O-NO_2$ $H_2-C-O-NO_2$

PENTAERYTHRITYL TETRANITRATE (PETN)

$O_2N-O-CH_2$, $O_2N-O-CH_2$ > C < CH_2-O-NO_2, CH_2-O-NO_2

Indications: For the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

Precaution: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

Side effects: No serious side effects have been reported. In sublingual therapy, a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound. Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

Supplied: 10 mg. Tablets (scored). Also available in 5 mg. and 15 mg. scored tablets in addition to Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital Tablets (scored).

10 mg. q.i.d. oral or
5 mg. q.i.d. sublingual
suggested starting regimen

improves exercise tolerance in angina pectoris patients

Cardilate®

(erythrityl tetranitrate)

the beta-adrenergic blocking agent

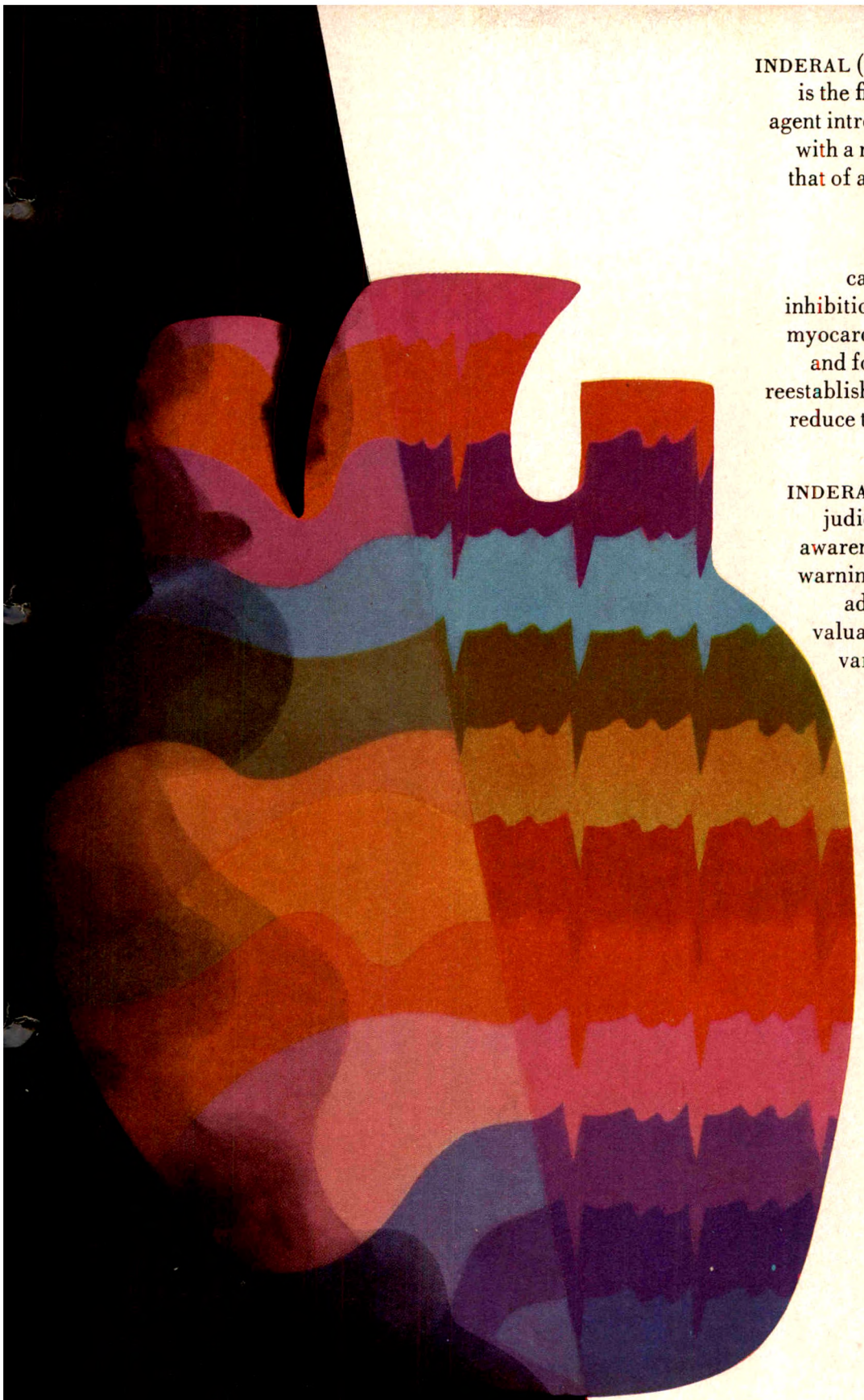
Inderal®

Brand of

propranolol hydrochloride

10 mg. and 40 mg. tablets

controls cardiac arrhythmias
and symptoms of hypertrophic
subaortic stenosis



INDERAL (propranolol hydrochloride) is the first beta-adrenergic blocking agent introduced into clinical practice, with a mode of action different from that of any agent previously used for cardiac arrhythmias.

INDERAL blocks access of catecholamines by competitive inhibition at beta-receptor sites in the myocardium. It reduces cardiac rate and force of contractions, and may reestablish normal rhythm. It may also reduce the frequency and severity of paroxysmal attacks.

INDERAL is a potent agent requiring judicious use. Administered with awareness of the contraindications, warnings, precautions, and possible adverse reactions, it provides a valuable tool in controlling a wide variety of cardiac arrhythmias, including some refractory to other drugs.

Inderal® (propranolol hydrochloride) is useful in a wide variety of cardiac arrhythmias

paroxysmal atrial tachycardia

sinus tachycardia and extrasystoles (atrial and ventricular)

atrial flutter and fibrillation

tachyarrhythmia of digitalis intoxication

tachyarrhythmias associated with anesthesia (in selected cases)

ventricular tachycardias (when conversion technics are not available)

also recommended in the management of
hypertrophic subaortic stenosis
pheochromocytoma

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See following page for prescribing information.

Inderal®
(propranolol hydrochloride)

BRIEF SUMMARY

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than second degree or total heart block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see under WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL, *i.e.* some patients with congestive failure exhibiting rapid heart rates due to a strong sympathetic component, with inadequate response to maximum doses of digitalis and diuretic, may be improved by the cautious addition of INDERAL to the treatment regimen; 7) in patients receiving anesthetics that produce myocardial depression such as chloroform and ether; 8) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a significant component in supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

In frank or incipient congestive failure, therefore, treatment with INDERAL should be carried out cautiously and preferably under the protective cover of concurrent digitalization. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues to progress, INDERAL therapy must be immediately withdrawn; (b) however, if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

PATIENTS PRONE TO HYPOGLYCEMIA: Caution should be exercised in the administration of INDERAL to patients subject to spontaneous hypoglycemia or to diabetics (especially labile diabetics) receiving insulin or oral hypoglycemic agents. Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pulse pressure changes) of acute hypoglycemia.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed when INDERAL is introduced into the treatment regimen. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity.

Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

In the majority of patients INDERAL (propranolol hydrochloride) is well tolerated, and side effects have been transient in nature, rarely necessitating withdrawal of therapy. Nausea, vomiting, lightheadedness, mild diarrhea, constipation, and mental depression (manifested by insomnia, lassitude, weakness, and fatigue) have been observed during the course of clinical investigation. One case of mental depression which progressed to a catatonic state was returned to normal when the drug was discontinued. Isolated cases of erythematous rash, paresthesia of the hands, fever combined with aching and sore throat, visual disturbances, and hallucinations have also been reported. Rarely, respiratory distress and laryngospasm have been reported following intravenous administration.

Elevated blood urea levels have occasionally been observed in a few patients with severe heart disease, and it is suspected that these high values were due to the renal status of the patient rather than a result of therapy. Similarly, elevated serum transaminase levels have occasionally been observed, but in no case was there any clinical or other laboratory evidence of hepatic dysfunction. One case of nonthrombocytopenic purpura and one case of thrombocytopenic purpura have been reported from abroad in patients who were receiving other drugs in addition to INDERAL. Three instances of reversible alopecia coincident with INDERAL administration have been reported; relationship to the drug has not been established.

DOSAGE AND ADMINISTRATION

The oral route of administration is preferred.

ORAL

Arrhythmias—10-30 mg. three or four times daily, before meals and at bedtime.

Hypertrophic Subaortic Stenosis—20-40 mg. three or four times daily, before meals and at bedtime.

Pheochromocytoma—Preoperatively—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg. daily in divided doses.

INTRAVENOUS

The usual dose is from 1-3 mg. administered under ECG monitoring. The rate of administration should not exceed 1 mg. (1 cc.) per minute. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. Once an alteration in rate of rhythm is recorded, it is advisable to give no further INDERAL until the full effect is observed. Depending on the response, a second dose may be repeated after two minutes. Additional medication should not be given in less than four hours. Therapy with oral dosage is advisable as soon as possible.

NOTE: Should excessive bradycardia occur, atropine 0.5-1.0 mg. should be administered intravenously.

SUPPLIED

INDERAL® (propranolol hydrochloride)

TABLETS—No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

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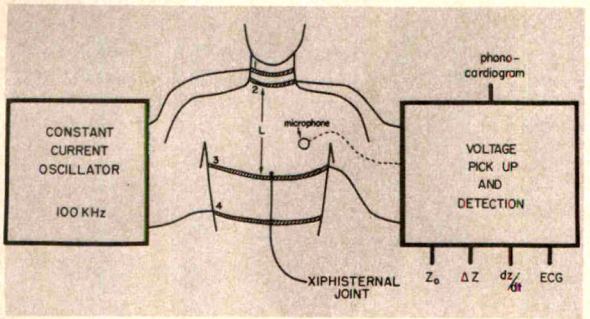
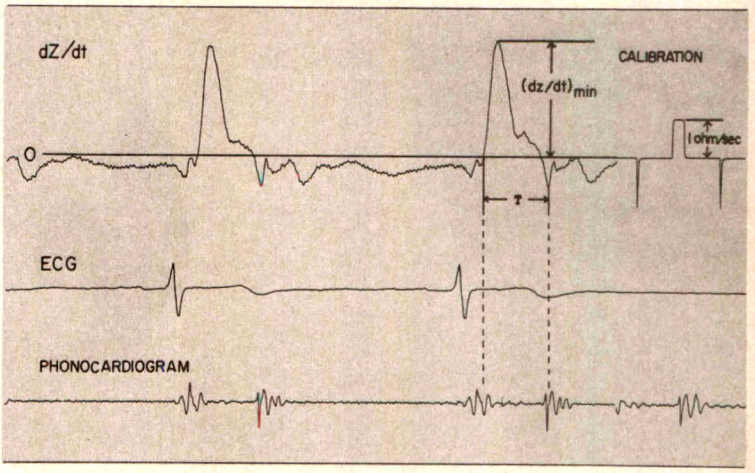
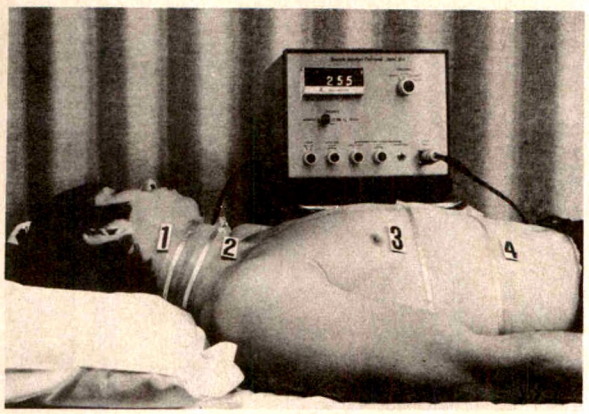
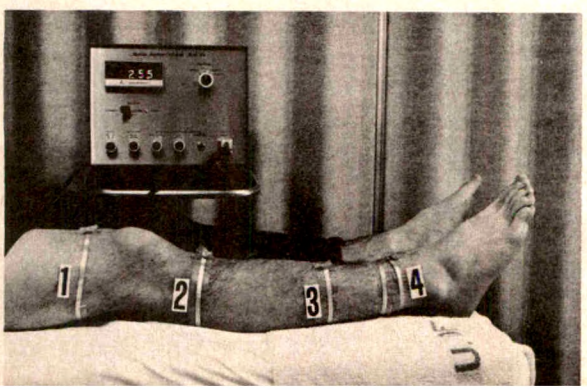






Z_0 = Total impedance between leads 2 and 3
ΔZ = Impedance Change during Cardiac Cycle
dZ/dt = First time derivative of ΔZ
ECG signal from leads 1 and 4
Phonocardiogram with two frequency bands
T = Ventricular Ejection time



APPLICATIONS

I. Z_0 for detection of pulmonary edema or changes in total thoracic fluid volume

II. ΔZ, dZ/dt and ECG to monitor mechanical and electrical cardiac parameters

III. A safe and rapid means to observe peripheral circulation

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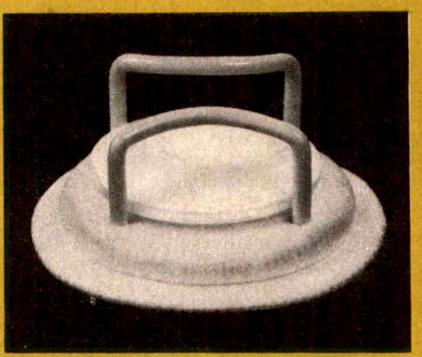
90°
C=3.146
$S = \frac{W}{2Z_1}(1-x)^2$
$\frac{1}{P}\int_S \int_O$

the elements of a vital decision



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REFERENCES:

[1]Cooley, D.A., Bloodwell, R.D., Okies, J.E., et al. Long-term results after cardiac valve replacement: clinical experience with 2,097 patients. Prosthetic Heart Valves. Proceedings of the Second National Conference on Prosthetic Heart Valves, 1969, ed. by Lyman A. Brewer III, M.D. pp. 530-39.

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[6]Vogel, J.H.K., Paton, B.C., Overy, H.R., et al. Advantages of the Beall valve prosthesis. Chest *59*:249-53, 1971.

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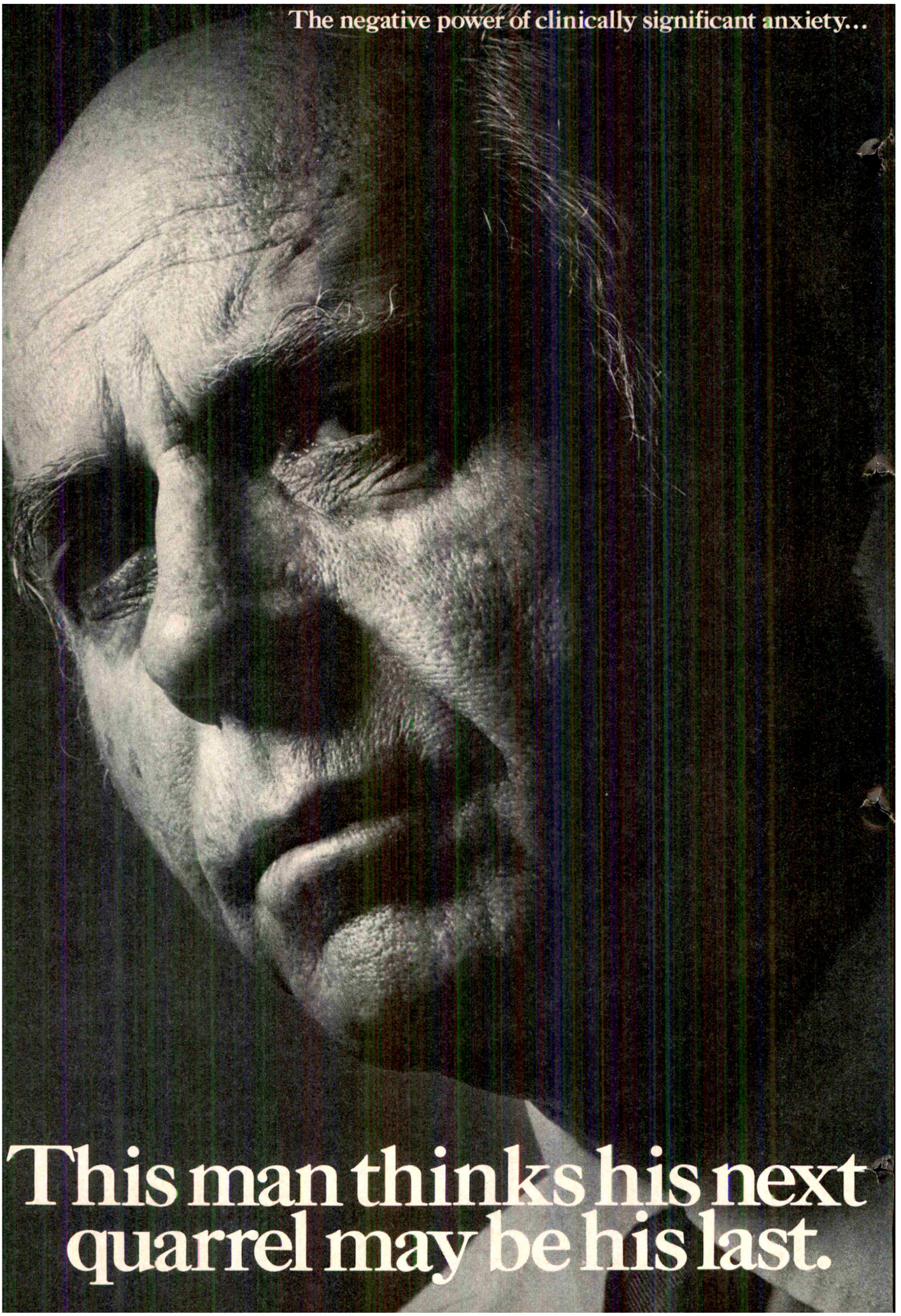
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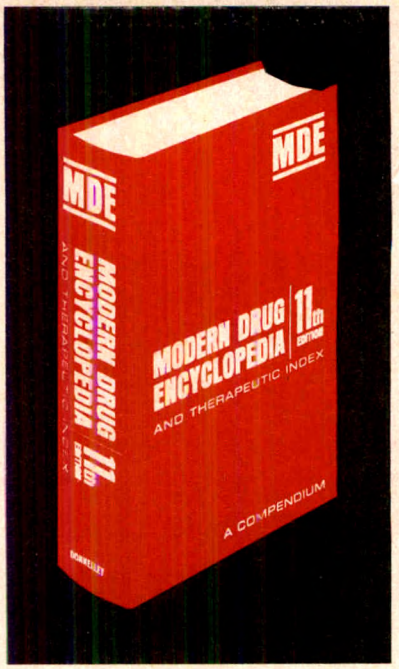

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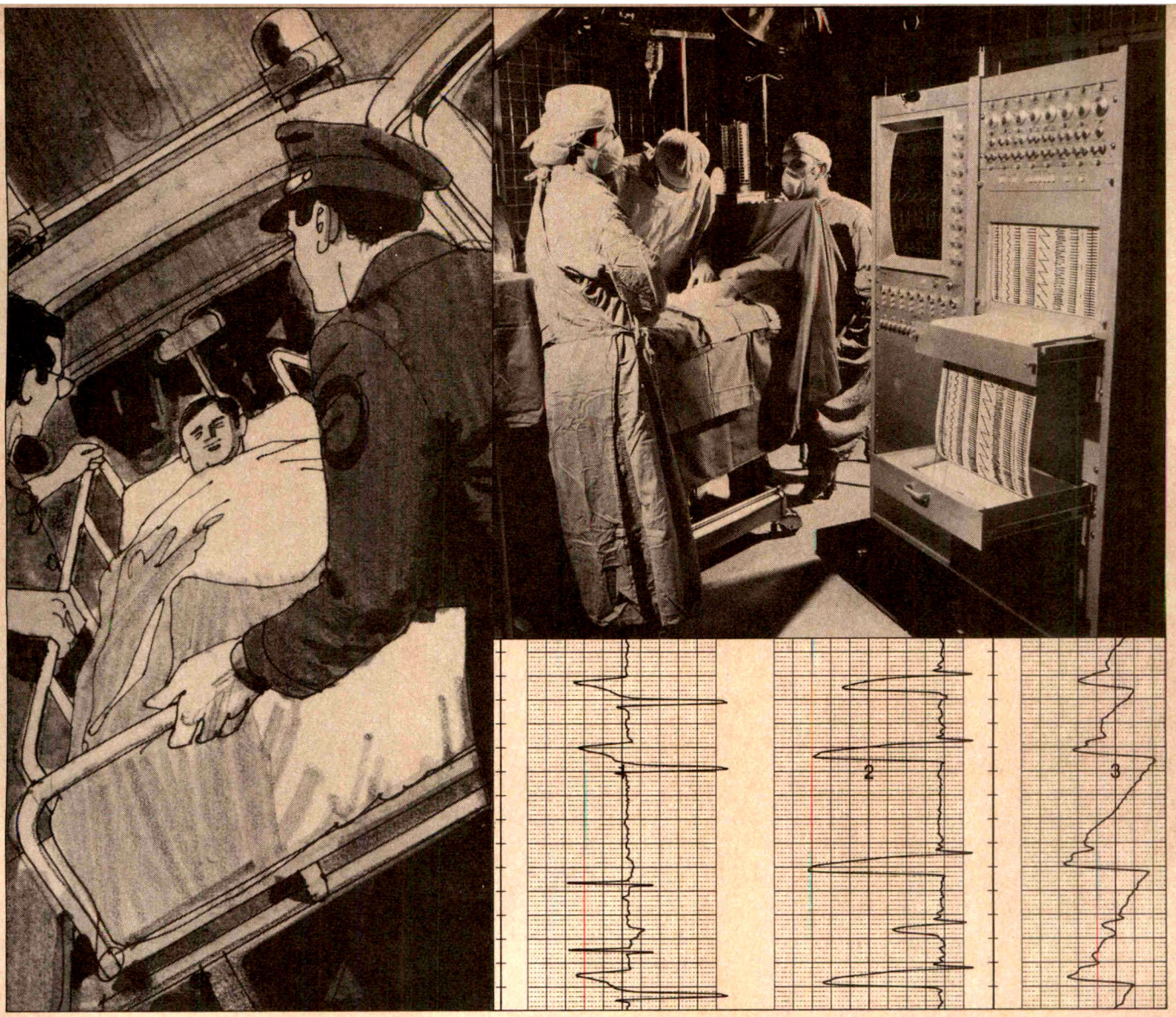

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By **Edward K. Chung,** M.D., Professor of Medicine and Director of Electrocardiographic Laboratory, West Virginia University School of Medicine.

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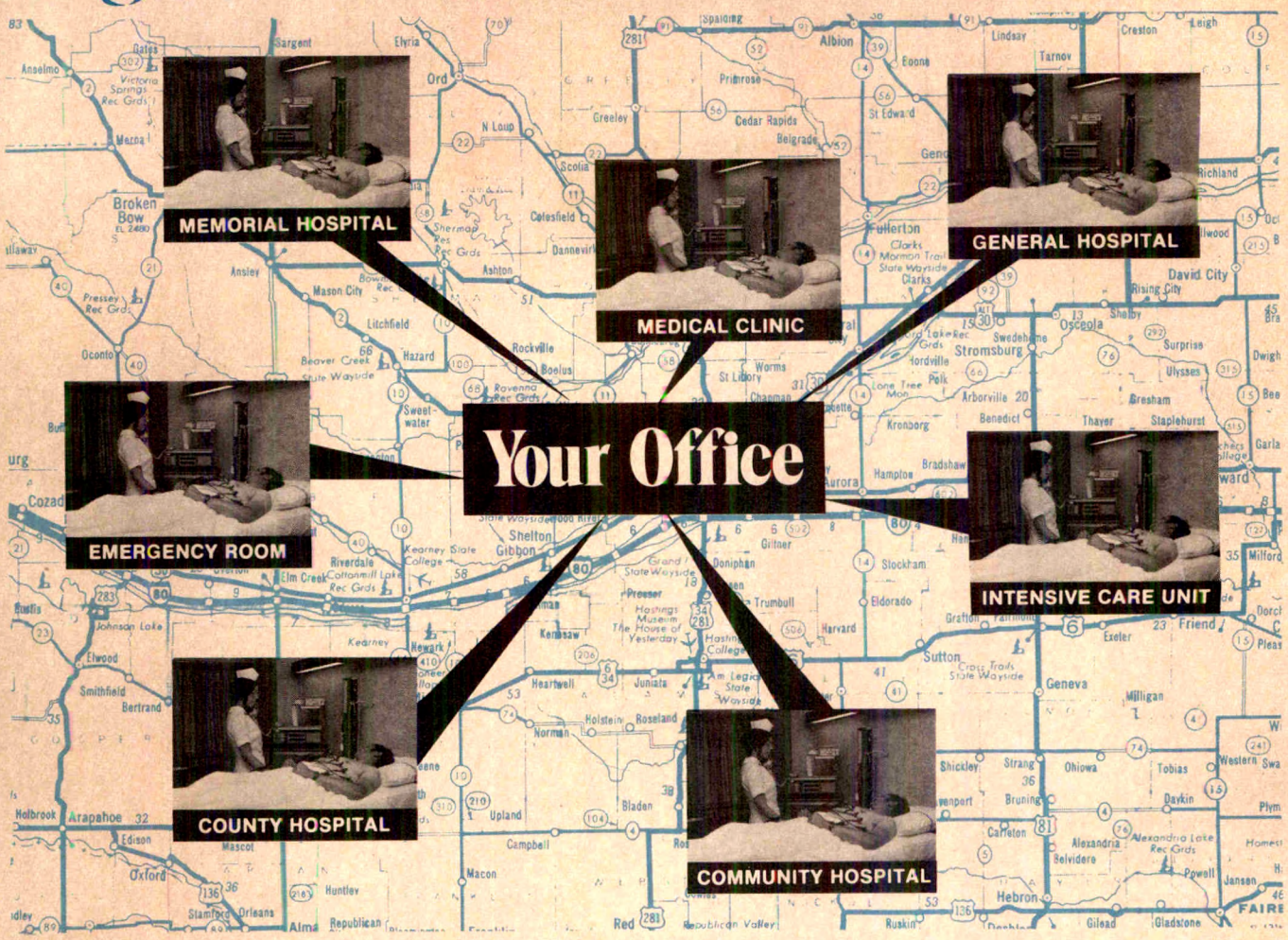

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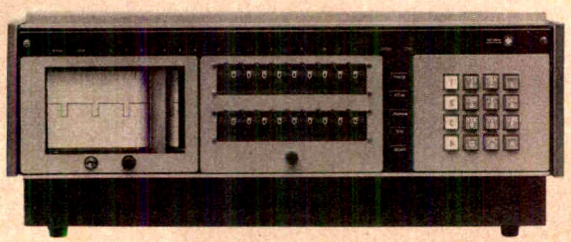

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Intracoronary Balloon—A New Model for Induction of Myocardial Ischemia*

TO THE EDITOR: At the present time there is serious criticism of all techniques employed for the induction of experimental coronary occlusion. We attempted to develop a new model for selectively occluding a specific coronary artery in the animal with a closed chest. Our new technique enables us to simulate the clinical condition of partial or complete localized occlusion of a specific coronary artery or its branches which can be terminated at will. Such a model provides a meaningful method for studying the function, metabolism and viability of an ischemic myocardium. It also permits a comprehensive technique for the study of cardiac arrhythmias during ischemia.

The following is a brief description of the new technique which we have developed to produce localized reversible coronary occlusion in the dog.

1. Selective coronary angiography is performed by introducing a pre-shaped thin wall no. 7F Teflon® cannula by way of the carotid artery into the left or right coronary artery. Cineangiograms or spot films are taken by injecting a 75 percent Hypaque® solution to delineate the coronary vasculature. Based on these spot films a specific branch of a vessel is selected for occlusion.

2. A no. 2 or 3F (0.8 to 1.0 mm outer diameter) catheter that as a balloon at the tip is threaded through the lumen of the angiographic cannula and advanced under fluoroscopic control into the desired location within the chosen coronary artery. Its passage into specific branches is facilitated by inserting a stylet which stiffens the catheter. Once the balloon catheter is in place the cannula is then withdrawn from the coronary ostium. The balloon catheter has a metallic tip which permits radiologic visualization of the balloon location. This tip also acts as an electrode to record the electrocardiographic potentials or as a pacemaker.

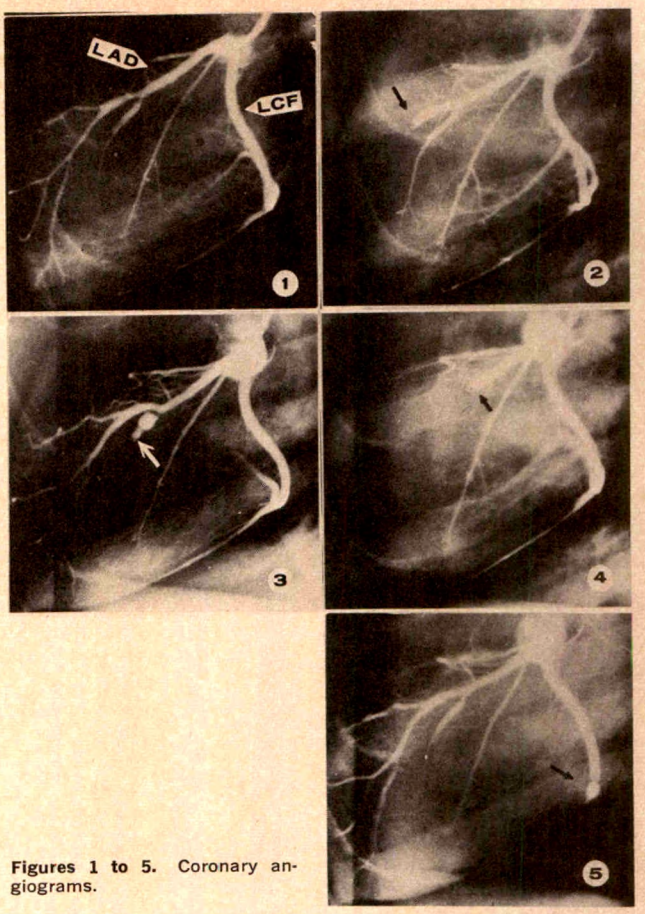
3. The balloon is partially or totally inflated to the dimensions of the artery by injecting 50 percent Hypaque (0.03 to 0.08 ml), after which the balloon catheter is sealed off. The balloon can be kept in its expanded state without leakage. Repeat coronary angiograms are immediately made to confirm the location of partial or complete occlusion of the coronary artery.

4. Ischemia induced by inflating the balloon can be subsequently reversed by deflation to reperfuse the ischemic myocardium.

5. A second lumen in the center of the catheter provides communication with the occluded region of the coronary artery for measurement of retrograde coronary arterial pressures, blood sampling from, and injection of pharmacologic agents into the artery distal to the point of occlusion.

Preliminary results: To date, the intracoronary balloon technique has been employed in 20 dogs to induce occlusion. No difficulty was experienced in inserting and locally positioning the balloon to provide occlusion of any of the three main coronary arteries as well as their branches.

*This study was supported by National Institutes of Health Contract PH 43-68-1333 from the National Heart and Lung Institute, Bethesda, Md.



Figures 1 to 5. Coronary angiograms.

Figure 1 is a coronary angiogram obtained to visualize the left anterior descending (LAD) and circumflex (LCF) arteries. Figures 2 and 3 are angiograms obtained after occlusion (**arrow**) of 2 different branches of the LAD. Figure 4 shows occlusion of the main left anterior descending artery and Figure 5 of the left circumflex artery.

Eliot Corday, MD, FACC
Tzu-Wang Lang, MD, FACS
Carlos Crexells, MD
Samuel Meerbaum, PhD
Los Angeles, California

Systemic Hypertension and Aortic Stenosis

TO THE EDITOR: The article "Severe Valvular Aortic Stenosis in Patients over 65 Years of Age" by Roberts, Perloff and Costantino (Amer J Cardiol 27: 497–506, 1971) provides an interesting perspective of aortic stenosis in the elderly. Their conclusion, however, that "systemic systolic hypertension can result in a comparatively small pressure gradient despite severe

left ventricular outflow obstruction" is not warranted by their data or consistent with hemodynamics. Inherent in the orifice equation, as stated by Gorlin and Gorlin in 1951 and supported by numerous hemodynamic studies, is the conclusion that aortic valve gradients are dependent only upon transvalvular flow, orifice area and cardiac output when ejection seconds per minute are unchanged. It is common in advanced valvular disease of any type to see relatively small gradients produced by low output despite severe stenosis. This is because gradient decreases with the square of flow, so that halving the cardiac output results in a gradient only one-fourth of the original value. Orifice area is independent of the actual levels of left ventricular and aortic pressure but varies inversely as the square root of their systolic difference.

Thus, it may be that the presence of systolic hypertension results in a left ventricular-aortic gradient at a higher level of left ventricular pressure, but if the mean gradient itself is smaller, it can only mean that flow is less or that the effective orifice area is not so small. It is possible that a problem is incurred in coronary blood flow because of the higher level of left ventricular pressure (and, presumably, oxygen consumption), and this might reduce cardiac output, but no data are presented that might clarify this point.

Philip O. Ettinger, MD, FACC
Newark, New Jersey

The Author Replies

Ettinger is concerned with the effect of systemic hypertension in the presence of discrete aortic stenosis. In reference 9 of our paper (Perloff et al: Circulation 35: 347–357, 1967) some comment was made in this regard: "The increase in brachial arterial systolic pressure induced by angiotensin infusion was accompanied by change in the left ventricular systolic pressure that was similar in direction but generally less in degree. The aortic gradient consequently fell as a rule. An already elevated systolic pressure proximal to a stenosed aortic valve may approach its physiological maximum during administration of angiotensin. Accordingly, a rise in pressure distal to the stenotic aortic orifice, which acts as a resistance in series, may not be readily transmitted into a quantitatively parallel rise in left ventricular systolic pressure. Although, the response of the gradient to acute elevations in aortic pressure need not apply to patients with chronic elevations, it may, nevertheless, be advisable to interpret an aortic gradient in the context of the level of systemic systolic pressure. Should persistent systolic hypertension reduce an aortic gradient, the degree of obstruction may be underestimated if the pressure difference were taken as the index of severity."

This observation is, by no means, at odds with Ettinger's correct comment that aortic valve gradients depend upon transvalvular flow, orifice area, cardiac output, and the like. We now have under study a number of patients with naturally occurring aortic stenosis and systemic hypertension as well as a larger series with acutely induced systemic hypertension (pharmacologic intervention). Systemic hypertension, as pointed out in our paper, may not only influence the aortic gradient and the length and frequency composition of the systolic murmur, but also may influence the arterial pulse regarding rate of pressure development and pulse pressure.

Joseph K. Perloff, MD, FACC
Washington, D. C.

Alcohol Ingestion by Mice

TO THE EDITOR: In the paper entitled "The Effect of Ingestion of Ethyl Alcohol, Wine and Beer on the Myocardium of Mice (Amer J Cardiol 27, 522–528, 1971), Burch et al. conclude that "These studies show that alcohol will produce myocardial damage in mice even if they are properly fed."

The animals consumed average amounts of beer, 5, 15 or 20 percent ethyl alcohol ranging from 4.0 to 7.5 ml daily. One group was given wine (20 percent ethyl alcohol) and was fed only once a week; the other groups were offered the same commercially available brand of laboratory chow ad libitum. The quantities of beverage consumed according to the authors were equivalent to daily human consumption of 15.9 liters of beer, 12.5 liters of 5 percent alcohol, 11.9 liters of 15 percent alcohol, 9.5 liters of 20 percent alcohol or 9.7 liters of wine. The authors do not give comparable figures for the consumption of solid food, nor do the data provided give any opportunity for calculating the same. Nevertheless, it is surely abundantly evident from the figures cited that a large percentage of the total caloric intake of the experimental animals must have been derived from the alcohol consumed in various forms.

Ethyl alcohol per se and most of the beverages containing it, including wine and beer, although rich in calories are almost completely devoid of any significant amounts of essential amino acids, vitamins or other vital food factors including a number of trace elements. Yet the simple caloric stress imposed by alcohol on the metabolic process of every organ of the body, including the heart, requires additional essential food factors and vitamins in order to metabolize the calory-rich alcohol ingested.

Commercially available foods for laboratory animals are guaranteed to contain the minimal amounts or more of all known vitamins necessary for the normal metabolism of the calories supplied by the chow itself when it is the sole source of energy for the animal. However, levels of these factors above this criterion are not known and vary considerably from time to time.

That hepatic injury in rats consuming alcohol (25 to 50 percent of total calories) is largely if not entirely caused by relative nutritional deficiencies has been well documented,[1] even though the possibility of some remaining direct hepatotoxic action is still postulated by some. To protect the liver from the additional stress of "nutritionally empty" calories derived from the prolonged consumption of alcohol by rats, the rats must simultaneously be offered a so-called "super-diet"[2] which contains sufficient amounts of all known food factors, vitamins and amino acids for the metabolism not only of the calories supplied by the food itself, but also for those derived from the otherwise "nutritionally empty" sources of alcohol. Commercially available laboratory food is quite unable to supply these amounts of extra vitamins and food factors. Resort must be made

to carefully formulated semi-synthetic food mixtures in order to maintain optimal nutritional conditions for alcohol-consuming animals.

In view of the foregoing, I respectfully submit that the experimental design employed by Burch et al. does not guarantee that the animals were "properly fed" and does not establish that the alcohol was a direct cardiotoxin. Instead it may well have induced a number of relative, but damaging, deficiencies of essential food factors.

W. Stanley Hartroft, MD, PhD, FAAC
Honolulu, Hawaii

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TO THE EDITOR: I believe that clarification is in order by Burch et al. with regard to the comparative figures for the human consumption of beer, wine and ethanol.

Using proportional calculations, the figure for the human consumption of water would be 18.1 liters! It would seem highly unlikely that these are true or relevant. Needless to say, any long-term study attempting to draw correlative implications would be highly suspect for lack of "reasonable" ethanol, wine or beer ingestion. Assuming a chronic ethanolic ingests 0.5 to 1 liter (1 to 2 pints) per day, it would appear that a similar corresponding amount might be fed to the mice.

Thomas B. Graboys, MD
Boston, Massachusetts

The Author Replies

We were aware of the possible nutritional aspects of our studies on the effect of ingestion of ethyl alcohol, wine and beer on the myocardium of mice. For that reason a group of mice were intentionally fed an inadequate diet, receiving food only 1 day per week while drinking 20 percent alcohol as wine. Those animals had fewer changes in the myocardium than the other animals that ate the same food daily on an ad libitum basis. In view of this, malnutrition was not an important factor, if one at all, in the production of the changes observed.

George E. Burch, MD, FACC
New Orleans, Louisiana

Atrial Dissociation

TO THE EDITOR: It was a surprise to read Chung's article ("A Reappraisal of Atrial Dissociation," Amer J Cardiol 28:111–117, 1971) and to see absolutely no mention of the excellent observations of Higgins et al., who wrote about the true nature of "atrial dissociation" in the July 1966 issue of the Journal (Amer J Cardiol 18:132–139, 1966).

In the past 2 months we have had the opportunity to see 4 cases of such an abnormality. Two sets of distinct P waves could be seen in leads II, III and aVF, 1 conducting to the ventricles and 1 with no relation to other atrial or ventricular events. Both sets of P waves were upright in these leads. It was obvious that the independent P wave was identical with the respiratory rate, no matter how rapid. The rates were between 40 and 80/min.

All of these patients died within days of respiratory failure secondary to chronic obstructive bronchiopulmonary disease with congestive failure.

In proof that the extra "P" waves were caused by respiratory muscle events, intubation with opiate sedation for initial respiratory rate control caused their immediate disappearance. Extubation was followed with the reappearance of tachypnea and obvious exhausting respiratory efforts. The reappearance of these dissociated P waves at the respiratory rate was observed.

Like Chung, we believe the appearance of this electrocardiographic finding is ominous. Unlike Chung, we believe it is most often if not always due to electrical events of accessory muscles of respiration.

Ralph G. Oriscello, MD
Edward G. Williams, MD
Elizabeth, New Jersey

The Author Replies

It is not unexpected that some investigators still doubt the existence of atrial dissociation.

I do agree that various artifacts and rhythmic movement of noncardiac muscles such as in Parkinsonism or respiratory failure may produce electrocardiographic findings similar to those of atrial dissociation. Therefore, true atrial dissociation should be distinguished from these findings especially when dealing with slow unilateral atrial rhythm. However, in the past several years, various clinical studies have shown unequivocal evidence of atrial dissociation. For example, transitional electrocardiographic changes from normal sinus rhythm to unilateral atrial fibrillation followed by uncomplicated atrial fibrillation were observed in a patient with cardiomyopathy (Fig. 3 to 5 of my paper). Another patient demonstrated transitional changes from sinus rhythm with first degree atrioventricular block to unilateral atrial flutter, followed by uncomplicated atrial flutter (Fig. 6 and 7). Unilateral atrial tachycardia in the presence of sinus rhythm followed by sinus arrest (Fig 2) is another unequivocal example of atrial dissociation. The purpose of my paper was to reemphasize the true existence of such interesting arrhythmias.

Edward K. Chung, MD, FACC
Morgantown, West Virginia

Clinicopathologic Features of the Heart in Reye's Syndrome

TO THE EDITOR: The findings of Morales et al. as reported in their paper entitled, "Pathology of the Heart in Reye's Syndrome" (Amer J Cardiol 27:314–317, 1971) parallel many of the findings in our study.[1] Although the findings in their cases were confined pri-

marily to the Purkinje cells, some of the cases in our series showed extensive changes in the ventricular myofibers. These included diffuse small droplet fatty accumulation, vacuolar changes and myocytolysis. Interstitial edema and focal hemorrhage were also present. Concurrent with these histopathologic changes, we have reported clinical or electrocardiographic findings, or both, of both myocardial injury including marked S–T segment changes in dysfunction including arrhythmias which the authors predicted might occur.

From a histopathologic standpoint, many of these changes in the heart would be classified as degenerative, which implies that they have developed as the result of decreased energy production by the cell. Reye's syndrome with its features of hypoxemia,[2] hypoglycemia[3] and, most importantly, lipolysis and mobilization of fat[4] that would result in the confrontation of the cardiac cells with the potential endogenous toxins, fatty acids,[5] provides an adequate set of circumstances that could result in decreased energy production with subsequent cellular degeneration and dysfunction. However, regardless of pathogenesis the physician should be alerted to the possible occurrence of both cardiac degeneration and dysfunction in Reye's syndrome.

The author's ultrastructural picture of the lipid "droplet" (their Figure 7) has not been (in our experience) the ultrastructural appearance[4] of the major portion of the accumulated lipid in Reye's syndrome. Furthermore, we have observed similar electron dense figures within mitochondrial-like structures in such cases and have interpreted these as structural lipid resulting from the breakdown of mitochondria. Finally, we suggest that the histologically demonstrable lipid in Reye's syndrome which by histochemical and ultrastructural means has been shown to be consistent with neutral lipid and by extraction procedures to be predominantly triglycerides[4,6] is not responsible for the degenerative changes. Instead we feel that fatty acids, one metabolite necessary for the formation of triglycerides, is responsible for the changes as previously mentioned. In this same light it is worth noting that fatty acids have been implicated in the production of cardiac arrhythmias.[7]

R. E. Brown, MD
G. E. Madge, MD
Richmond, Virginia

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The Author Replies

Interpretation of electron microscopic findings is based on observation of a number of photographs, but in publishing "Pathology of the Heart in Reye's Syndrome" we were asked by the editor to limit the number of electron micrographs. It is possible that the one chosen to demonstrate fat droplets within dilated endoplasmic reticulum was a poor one. I am submitting an additional photograph (Fig. 1) which demonstrates (to our satisfaction) that the inclusions within the dilated sarcotubular system are indeed lipid droplets. Myocytolysis was not a feature in our cases.

Figure 1. Electron micrograph of heart muscle. × 22,000, reduced by 28 percent.

The pathogenesis of the cardiac lesions suggested by Brown and Madge is certainly worth consideration. We found more pronounced alterations in the subcellular organization of the liver, in particular of the mitochondria and endoplasmic reticulum, which led us to postulate the existence of a block in lipid metabolism at this level with secondary accumulation of triglycerides and fatty acids.[1]

A. R. Morales, MD
Detroit, Michigan

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Book Reviews

My Life and Medicine—An Autobiographical Memoir, by Paul Dudley White, MD. Boston, Gambit, 1971, 269 pages, $6.95

The memoirs of Paul Dudley White portray the life history of a great human being—his thoughts, his teaching activities, his contributions to cardiology as a scientific discipline and his lifelong concern for world peace. This history is interwoven into a literary fabric which affords the reader a profitable, stimulating experience. The chronology of personal events never reflects egotism. The qualities of sympathy, determination, insight and profound skill reveal a man who possesses the highest attributes in medicine and in society.

Dr. White's early training by his physician-father, his educational experience at Harvard Medical School and his interests in pediatrics and internal medicine prepared him for the opportunity to study under the world's greatest cardiologists—Sir James McKenzie, Sir Thomas Lewis, John Parkinson and others in London. In 1914 he returned to Boston and set up an electrocardiographic laboratory in the basement of the Massachusetts General Hospital.

Soon thereafter, Dr. White, with Dr. Richard Cabot, began the classification of heart disease according to its origin, thus becoming a pioneer in the concept of preventive cardiology.

World War I found him serving in Europe as a medical officer, and he later had a tour of duty in Macedonia, sponsored by the Red Cross. Returning to Boston, he fathered the beginnings of cardiology through practice, teaching and clinical research. He wrote the first American textbook on heart disease in 1929.

Dr. White's interest in the anatomy and physiology of large mammals brought interesting and profitable interludes in his life as he studied the action of the elephant's heart in Boston, and the heart of the grey whale, both in Alaskan waters and in the Pacific Ocean off the coast of Mexico.

During the 1940's and 1950's Dr. White pointed to the wider range of normal findings in man, and indicated that no man necessarily conformed to the so-called averages. He especially emphasized the wide variation in normal heart rate, heart size and blood pressure.

Following his retirement as an active director of the cardiac laboratory and cardiac clinics at Massachusetts General Hospital, his advice was widely sought and his activities as a consulting cardiologist and world traveler in the interest of the heart and global peace increased markedly.

The measure of the man and the physician is seen in his detailed account of President Eisenhower's heart attack. In the care of the President, his belief that both medical and lay communities should know the details of the illness and the status of the patient at all times established a precedent. He pointed out that recovery from a heart attack is possible and that long years of useful life may follow. The chapter on President Eisenhower's heart attack should be required reading for all.

The increasing incidence of coronary artery disease, especially in the young American, is emphasized. He shows that control of the greatest epidemic the world has ever known—coronary artery disease—can be attained by physical fitness, prudent dieting, avoidance of tobacco and the lessening of tension.

Throughout the book it becomes unmistakably clear that most of the advances in cardiology were heralded by the mind of Dr. Paul Dudley White.

George C. Griffith, MD, FACC
La Cañada, California

Coronary Heart Disease, edited by H. I. Russek, MD and B. L. Zohman, MD. Philadelphia, J. B. Lippincott, 1971, 502 pages, $20.00

This volume consists of a discussion of the various aspects of coronary artery disease presented at a symposium sponsored by the American College of Cardiology and St. Barnabas Hospital in New York City on December 13 to 15, 1969. The chapters are written by some of the most famous names in American medicine. Discussed are the recent concepts of the anatomy of the coronary arteries with reference to their functional import and the location of obstructive disease of the coronary circulation. Discussion of pathophysiologic and pathogenetic factors is extensive and includes excellent chapters by Gregg on the physiologic factors which determine coronary blood flow and techniques for measurement of the coronary circulation by Gensini and associates. An excellent chapter by Katz considers the effects of ischemia and hypoxia upon the myocardium. Rosenman and Friedman present an informative discussion on the possible role of behavior patterns in proneness and immunity to coronary heart disease. Gudbjarnason and Bing contribute an excellent chapter on the metabolic changes in myocardial infarction. The diagnosis of ischemic heart disease is presented in considerable detail as is the long-term management of ischemic heart disease. The problems encountered in the acute coronary care unit are presented by Grace, Weil, Shubin, Killip, Kuhn and others. An excellent chapter is that on the management of heart block complicating acute myocardial infarction by Dack and Donoso. The surgical treatment for coronary artery disease is presented by Lillehei, Vineberg, Sones, Bailey and associates, with some dissenting opinions by Friedberg.

Some of the drawbacks in this volume are those which are frequently inherent in a compilation of data on various subjects by many different authors. These include variation in the emphasis placed on different topics, lack of uniformity of presentation, repetition of certain aspects, and variation in emphasis and methods of presentation of data.

In summary, this volume consists of an excellent compilation and review of the recent status of the subject of coronary heart disease and should be in the library of the cardiologist, internist and cardiovascular surgeon.

Samuel Bellet, MD, FACC
Philadelphia, Pennsylvania

Electronic Instrumentation. Theory of Cardiac Technology, by Lawrence W. Piller. Springfield, Ill., Charles C Thomas, 1970, 224 pages

The clinician and investigator concerned with disease or dysfunction of the circulation are highly dependent upon technology that involves devices for measuring some electrical or mechanical variable. The young cardiologist soon discovers, and sometimes too late, that in his practice of diagnostics and therapeutics he often stands at the mercy of a machine which is by no means absolute in its results or constant in its performance.

It has always been difficult to give guidance to the young physician entering the field of cardiology or pulmonary diseases on how to review the physics and electronics required to understand the potential shortcomings, distortions and variability of the instrumentation he will be using. It is even more difficult to provide such information to the technicians and technologists who operate and maintain the equipment. Mr. Piller has gone far to make this task of a director of a cardiovascular laboratory easier, in relation not only to the physician entering, for example, a fellowship in cardiology but also to the technical staff that are indispensable to him in his daily activities.

The book is divided into 3 parts and an appendix. It has an excellent though incomplete list of 75 citations in the bibliography. It was probably an oversight that Mr. Piller left out of this list the "Recommendations for Standardization of Leads and Specifications for Instruments" published by a Committee on Electrocardiography of the American Heart Association in 1967, a report which contains a great deal of technical electrocardiographic information which would be of interest to all physicians and technologists who might use Mr. Piller's book.

Part I, "Electronic Fundamentals," is presented in a clear style with simple line drawings which are most helpful in understanding the involved physics that medical students usually find distressingly elusive. For a technician with a good electronics background, it might, as the author indicates, be too elementary.

Part II, "Instrumentation Theory," is simply written and includes such items as the electrocardiograph, monitors, defibrillators, pacemakers, transducers, flowmeters and the like. Perhaps this part should also have included something about vectorcardiographs, pulmonary function testing devices and hemodialysis machines, but possibly it would have made the volume too large and too diverse. The same might be said for computer technology which is complementing all fields of electronic instrumentation as used in the study of the circulation.

Part III, which includes a discussion of safety considerations, is important, but the chapter on cardiopulmonary resuscitation might have been omitted since it is not quite pertinent in a book with this title.

In conclusion, this is a fine effort toward helping the growth and development of the cardiologic technologist, a relatively new and important component of the ever-growing team of physicians, surgeons, nurses and paramedical personnel concerned with the morbidity and malfunction of the circulatory system. Undoubtedly, subsequent editions of the book will be improved, but it can be recommended as it now stands for all technicians who will have anything to do with modern electronic medical instrumentation and also for medical students and fellows who have chosen to busy themselves with the modern measurement of circulatory variables.

Charles E. Kossmann, MD
Memphis, Tennessee

Cardiac Rehabilitation, edited by Lenore R. Zohman, MD and Jerome S. Tobis, MD. New York, Grune & Stratton, 1970, 248 pages, $12.75

Cardiac rehabilitation involves the restoration of a patient with heart disease to an optimal level of function, compatible with the degree of cardiac impairment; it also includes the maintenance of the patient at this level. The process of cardiac rehabilitation, then, is synonymous with excellent comprehensive care and is dependent on the skills not only of the physician but of many members of the health care team.

Zohman and Tobis review the physiologic and biochemical bases and the determinants of cardiac function, and describe procedures used to evaluate function and methods and programs designed to enhance function in patients with many varieties of heart disease. They specify that the diagnostic methods, specific drug regimens, surgical therapy, and the like for cardiac disease are beyond the scope of their book; however, since all these areas are so intimately involved both in evaluation and in enhancement of function of the cardiac patient, chapters or sections of this volume, appropriately placed, would complement the material presented in many standard textbooks on cardiology and cardiac surgery. Similarly, recommendations for evaluation of cardiac function, particularly serial evaluation in assessing the need for surgical intervention, or discussions of concomitant drug and physical activity programs to enhance function, would be valuable here. They would reinforce the authors' statements that the disciplines they emphasize constitute an integral part of acute and chronic cardiac patient care. They would also provide a basis for a much needed discussion of indications and contraindications for cardiac function (exercise) testing and physical activity training programs.

The authors document the physiologic changes associated with emotion, stress and physical activity. There is a good classification of the exercise tests used to evaluate cardiovascular function; the interpretation of the exercise electrocardiogram is presented in detail, and proper emphasis is given to the relation between exercise test results and job energy requirements. Although this book is obviously not intended as a "how to do it" manual for cardiac rehabilitation, but is rather a survey of the scientific basis and a sampling of methods and programs, it provides the type of comprehensive review particularly valuable for those beginning a cardiac rehabilitation effort. It is emphasized that cardiac impairment should not become cardiac disability; the concept of the health care team, the role of work evaluation units, the value of sheltered workshops and advantages of on-the-job patient monitoring are well reviewed. The authors appropriately recommend that physicians be as familiar with the use of an exercise prescription and a work prescription as they are with medication prescriptions.

Nanette K. Wenger
Atlanta, Georgia

Cardiovascular Bibliography of Selected Reviews

A Cooperative Program of the
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Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue of the Journal (Amer J Cardiol 28: 366–367, 1971).

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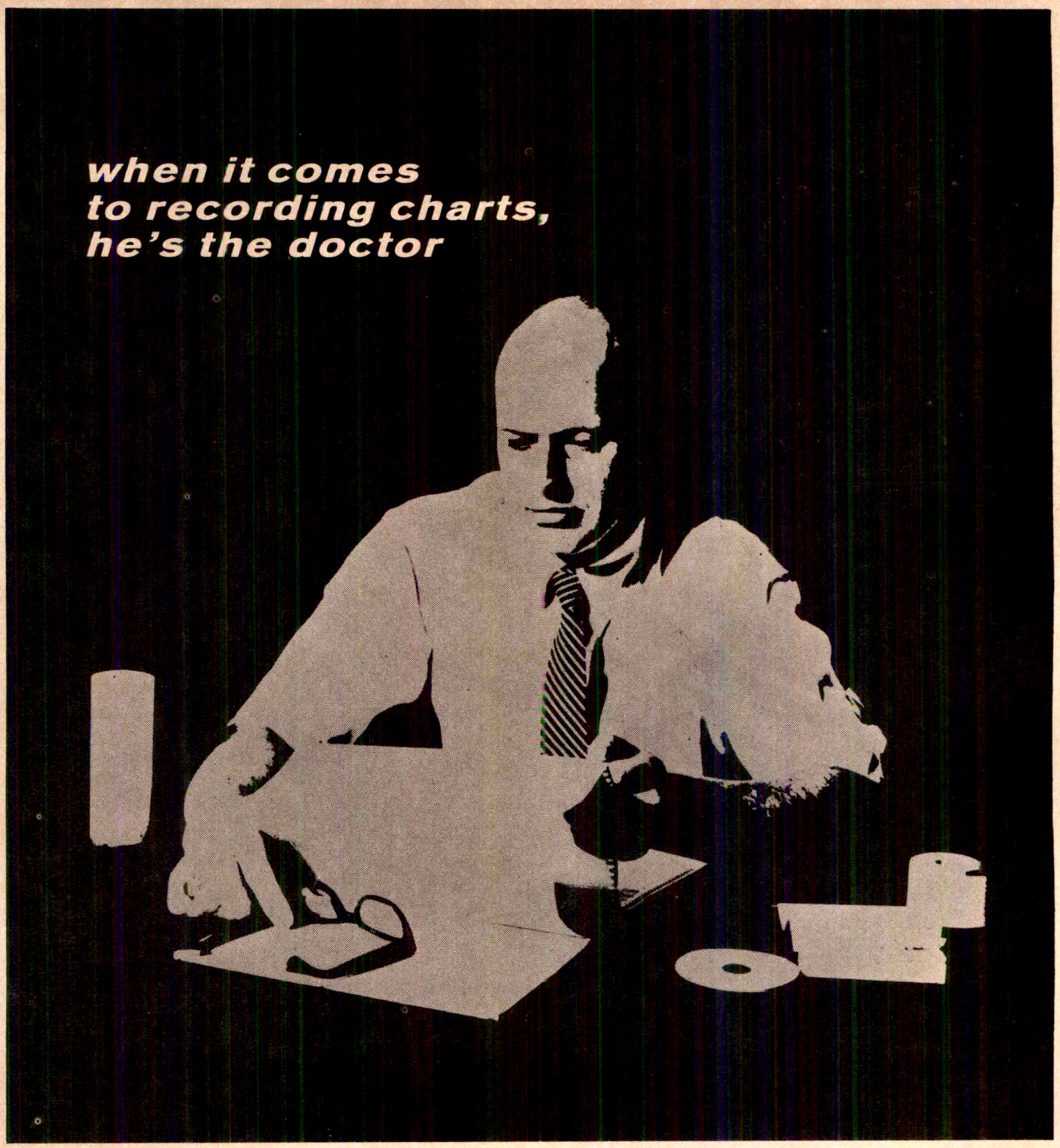

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American College of Cardiology News

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

FEB. 7–9 **The Acute Cardiac Emergency.** Robert S. Eliot, FACC and Gerald Chaplin, co-directors. Ponte Vidra Club, Jacksonville, Fla.

MAR. 20–22 **Electrocardiographic Interpretation of Arrhythmias: A Physiologic Approach.** Charles Fisch, FACC, director, Indiana University Medical Center, Indianapolis, Ind.

MAR. 20–25 **Consultants' Course in Cardiology.** Simon Dack, FACC, Arnold M. Katz, FACC and Robert S. Litwak, FACC, directors. Mount Sinai School of Medicine, New York, N. Y.

APR. 3–12 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 5–7 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 12–13 **The Total Coronary Care System—The Community and The Hospital.** Sylvan L. Weinberg, FACC, C. W. Immt and Joseph M. Wilson, FACC, co-directors. The Sheraton-Dayton Hotel, Dayton, Ohio.

APR. 17–20 **Current Concepts in Cardiology 1972.** Philip R. Akre, FACC and John A. Bower, MD, directors. Riviera Hotel, Las Vegas, Nev.

MAY 8–12 **The Medical and Surgical Treatment of Cardiovascular Disease.** J. Willis Hurst, FACC and W. Dean Warren, MD, directors. Co-sponsored by ACC and Council on Clinical Cardiology of the American Heart Association. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 12–13 **Computer Applications in Electrocardiography.** C. A. Caceres, FACC, director, Sheraton Park Hotel, Washington, D. C.

MAY 18–19 **Heart Sounds and Murmurs: An Audiovisual Presentation.** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, Ind.

MAY 25–27 **A Critical Approach to Cardiovascular Diagnosis.** Arthur Selzer, FACC, director. Jack Tar Hotel, San Francisco, Calif.

SEPT. 8–10 **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, director. Queen Elizabeth Hotel, Montreal, Quebec, Canada.

SEPT. 13–15 **The Clinical Manifestations of Congenital Heart Disease from Birth through Adulthood.** Joseph K. Perloff, FACC and Antonio C. DeLeon, Jr, FACC, directors. Georgetown University Medical Center, Washington, D. C.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director. Hahnemann Medical College, Philadelphia, Pa.

OCT. 10–14 **Vectorcardiography.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

DEC. 8–10 Henry I. Russek, FACC, director. Americana Hotel, New York, N. Y. Title unavailable.

Advance registration forms for these courses may be obtained by writing to Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Advance Programs*

APRIL 12, 13, 1972

Dayton, Ohio

THE TOTAL CORONARY CARE SYSTEM—THE COMMUNITY AND THE HOSPITAL

Program director:
SYLVAN L. WEINBERG, MD, FACC
Dayton, Ohio

Program co-directors:
WILLIAM G. CASSEL, MD, FACC
C. W. IMM, MD
JOSEPH M. WILSON, MD, FACC
Dayton, Ohio

Program committee:
HOMER CASSEL, MD, FACC
DAVID R. MARCUS, MD
MAXENE MILLER, BS, RN
K. SINNATHAMBY, MD
Dayton, Ohio

This symposium is the fourth in a continuing series sponsored by The American College of Cardiology and The Good Samaritan Hospital in Dayton and designed to assess the status of coronary care concepts. The current program emphasizes the evolutionary trends which have moved from the circumscribed approach of a coronary care unit to a coronary care system which involves the community and the total hospital. In this context the patient enters the coronary care system with his first symptoms. His ultimate survival may depend on the effective operation of this system which will be described in detail during the course of this symposium. The faculty will be composed of outstanding contributors in the field who have, during the past several years, helped to shape current concepts in the coronary care system. The program format seeks to allow ample time for presentation and interchange of ideas among the faculty and participants. In addition, luncheon panels will deal with specific aspects of therapy in the management of acute coronary disease.

Faculty:

Drs. Siavosh Bozorgi, Dayton, Ohio; Homer D. Cassel, Dayton, Ohio; William G. Cassel, Dayton, Ohio; and Stuart M. Denmark, Dayton, Ohio; Mr. David L. Ford, Dayton, Ohio; Drs. Peter L. Frommer, Bethesda, Md.; William J. Grace, New York, N. Y.; L. Julian Haywood, Los Angeles, Calif.; C. W. Imm, Dayton, Ohio; Huascar E. Jessen, Dayton, Ohio; Louis Lemberg, Miami, Fla.; David R. Marcus, Dayton, Ohio; Miss Maxene Miller, Dayton, Ohio; Mr. William D. Nelligan, Bethesda, Md.; Dr. Leonard Scherlis, Baltimore, Md.; Mr. Earl E. Shelton, Dayton, Ohio; Drs. Kuddythamby Sinnathamby, Dayton, Ohio; John C. Stahler, Dayton, Ohio; H. J. C. Swan, Los Angeles, Calif.; Herman N. Uhley, San Francisco, Calif.; James V. Warren, Columbus, Ohio; Sylvan L. Weinberg, Dayton, Ohio; Joseph M. Wilson, Dayton, Ohio

Location:

All sessions will be held at the Sheraton-Dayton Hotel, Dayton, Ohio.

Enrollment:

Minimal and maximal enrollment has been established for this program. Advance registration is requested.

Fee:

Members of ACC and of Montgomery County Medical Society, $100; nonmembers, $125.

MAY 8–12, 1972

Atlanta, Georgia

THE MEDICAL AND SURGICAL TREATMENT OF CARDIOVASCULAR DISEASE

Sponsors:

The American College of Cardiology
and
The Council of Clinical Cardiology, American Heart Association
and
The Departments of Medicine, Surgery, Pediatrics, Pathology and Radiology, Emory University School of Medicine
in cooperation with
The Georgia Heart Association

Program directors:

J. WILLIS HURST, MD, FACC
W. DEAN WARREN, MD, FACC
Atlanta, Georgia

We invite you to join us in the introduction of the problem-oriented postgraduate course. The symposium represents the beginning of a new era in continuing medical education. The content of the program will be couched in the context of the problem-oriented approach to medical education and patient care as proposed by Weed and others.[1–4] As years go by and more physicians use the problem-oriented record as a tool for improving education and patient care, then postgraduate courses will become more responsive to the needs of the physician. Furthermore, the physician will be able to translate what he learns to the care of his patients with greater facility. This particular program is designed to emphasize the second, third and fourth steps in the problem-oriented logic system: Data base → Problem list → Initial plan → Progress notes.

1. Weed LL: Medical Records, Medical Education and Patient Care. Cleveland, Ohio, Case Western Reserve University Press, 1969
2. Bjorn and Cross: Problem Oriented Practice. Chicago, Modern Hospital Press, 1970
3. Hurst JW: How to implement the Weed system. Arch Intern Med, September 1971
4. The Problem-Oriented Record, Teaching Medicine and Patient Care (Hurst JW, Walker HK). MEDCOM, in press

Guest faculty:

Drs. W. Gerald Austen, Boston, Mass.; Roderick W. Childers, Chicago, Ill.; Joseph Lindsay, Jr., Washington, D. C. and James J. Morris, Jr., Durham, N. C.

Local faculty:

Drs. Dorothy E. Brinsfield, Vardaman M. Buckalew, Jr., Nathan H. Carliner, B. Woodfin Cobbs, I. Sylvia Crawley, James C. Crutcher, Mario Di Girolamo, Edward R. Dorney, William H. Fleming, Gerald F. Fletcher, Robert H. Franch, Charles A. Gilbert, Leon I. Goldberg, Michael B. Gravanis, Charles R. Hatcher, J. Willis Hurst, Spencer B. King, R. Bruce Logue, Kamal Mansour, John L. McNay, Jr., Robert D. Milledge, Donald O. Nutter, E. Alan Paulk, Jr., William H. Plauth, Jr., Paul H. Robinson, Robert C. Schlant, Jonas A. Shulman, Mark E. Silverman, Robert B. Smith III, John H. Stone, Panagiotis N. Symbas, Elbert P. Tuttle, Jr., Paul F. Walter, W. Dean Warren, Nanette K. Wenger, and Joseph A. Wilber

* Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Location:

All sessions will be held at the Royal Coach Motor Inn, Atlanta, Georgia.

Fees:

Members of ACC and the Council on Clinical Cardiology, $200; nonmembers, $250.

MAY 12, 13, 1972

Washington, D. C.

COMPUTER APPLICATIONS IN ELECTROCARDIOGRAPHY

Sponsor:

The American College of Cardiology

Program co-directors:

C. A. CACERES, MD, FACC
Washington, D. C.

LEONARD S. DREIFUS, MD, FACC
Narberth, Pennsylvania

The program is designed to review the latest clinical information pertaining to computers in electrocardiography. The overall purpose of the program is to focus on the clinical knowledge that has been acquired as a result of utilization of computers in electrocardiography. By May of 1972 there will be several centers of various types processing electrocardiograms for at least a year and a half. More are coming. The experiences and the current results will be of interest from screening to intensive care.

Many thousand electrocardiograms will have been computer-processed. The sessions will deal with programs available for clinical use, their problems and the ethics of utilization of computer-interpreted electrocardiograms. A component devoted to basics as it effects vectorcardiography and computers will be featured.

Computer detection of arrhythmias will be covered and will be as up to date as possible. The participants will obtain background in: (a) appropriate use of computer electrocardiography in clinical care; (b) appropriate use of computer electrocardiography as a research tool; (c) appropriate separation of engineering from clinical medicine requirements in computer electrocardiography; (d) the future development of ethical requirements; and (e) beginning structure for standardization in computer electrocardiography.

Faculty:

Drs. C. Batchlor, Washington, D. C.; M. Belson, Washington, D. C.; J. Cornfield, Pittsburgh, Pa.; Lamar Crevasse, Gainesville, Fla.; R. A. Dunn, Washington, D. C.; J. Enderle, Brussels, Belgium; Gerald Flichelli, Omaha, Nebr.; Samuel Fox, Washington, D. C.; W. K. Haisty, Washington, D. C.; Julian Haywood, Los Angeles, Calif.; Howard M. Hochberg, Cranbury, N. J.; Gerald Kein, Chicago, Ill.; Bernard Lown, Boston, Mass.; Henry Neufeld, Tel Aviv, Israel; G. Charles Oliver, St. Louis, Mo.; Kenneth Patton, Waltham, Mass.; Herbert Pipberger, Washington, D. C.; Leon Pordy, New York, N. Y.; Arthur E. Rikli, Columbia, Mo.; Otto Schmitt, Minneapolis, Minn.; Ralph E. Smith, Rochester, Minn.; R. Stratbrucher, Omaha, Nebr.; Anna Lea Weihrer, Washington, D. C.; and J. Willems, Washington, D. C.

Fees:

ACC members, $95; nonmembers, $115.

MAY 18, 19, 1972

Indianapolis, Indiana

HEART SOUNDS AND MURMURS: AN AUDIOVISUAL PRESENTATION

Sponsors:

The American College of Cardiology
and
Methodist Hospital Graduate Medical Center, Indianapolis, Indiana

Program director:

MORTON E. TAVEL, MD, FACC
Indianapolis, Indiana

In this program high fidelity tapes of various normal and abnormal sounds will be played into individual audiophones. Simultaneous visual records will be made on an oscilloscope and on paper for projection. The program will include discussion of the physiology and clinical significance of all these sonic phenomena, together with instruction on interpretation of phonocardiograms and external pulse records. Sounds will be presented as "unknowns" during some audience participation sessions.

Guest faculty:

Drs. Alberto Benchimol, Phoenix, Ariz. and Modestino Criscitiello, Boston, Mass.

Local faculty:

Drs. Richard W. Campbell and Milton Gibson

Fee:

ACC members, $70; nonmembers, $90.

News in Brief

New Members Elected

The following individuals were elected to membership in the American College of Cardiology on November 10, 1971 in the grade designated below:

Fellowship

AYERS, Charles R., MD, North Carolina
BACOS, James M., MD, District of Columbia
BURTON, Carl R., MD, Canada
CUDKOWICZ, Leon, MD, Pennsylvania
DAVACHI, Farzin, MD, Nigeria
EBERT, Paul A., MD, New York
EVANS, Gerald L., MD, Massachusetts
FINK, Myron, MD, Ohio
FISHMAN, Alfred P., MD, Pennsylvania
GAGO, Otto, MD, Michigan
GOODKIND, M. Jay, MD, Pennsylvania
GOPINATH, Nagarur, MD, India
GOULET, Claude, MD, Canada
HEIMLICH, Donald L., MD, New York
HERLOCHER, James E., MD, Michigan
HUSNI, Elias A., MD, Ohio
INDEGLIA, Robert A., MD, Rhode Island
KIMBALL, John T., Jr., MD, Colorado
LINDBERG, Evan F., MD, Minnesota
McGARVEY, Joseph F. X., MD, Pennsylvania
MALOOLY, Donald A., MD, Texas
MANLEY, John C., MD, Wisconsin
MARKS, Charles, MD, Louisiana
NAGLE, John P., Jr., MD, Washington
NIGHTINGALE, David S., MD, Kentucky
OAKLEY, Celia M., MD, England
OSTERMILLER, William E., Jr., MD, California
PIERCE, William S., MD, Pennsylvania
REEMTSMA, Keith, MD, New York
SALYER, John M., MD, California
SANO, Toyomi, MD, Japan
SHIRKEY, Albert L., MD, Oklahoma
SINHA, Sachchida N., MD, Illinois
SOBEL, Burton E., MD, California
SOTO, Benigno, MD, Alabama
SUMMERALL, Charles P., MD, South Carolina
SUZMAN, Moses M., MD, South Africa

TOMOMATSU, Tatsuya, MD, Japan
WESTURA, Edwin E., MD, Missouri

Associate Fellowship

ANTANI, Jayant A., MD, India
AUERBACH, Herman L., MD, Pennsylvania
CREWS, Thomas L., MD, Georgia
CUADROS, Hugo F., MD, Illinois
*DAVACHI, Ali A., MD, New York
DOUGLAS, John E., MD, Arkansas
DOWLUT, Ahmad, MD, Mauritius
EASON, Hamel B., MD, Tennessee
*FISCHER, Donald C., MD, Ohio
HARRIS, Clifford N., MD, California
HOLLAND, William E., MD, Virginia
HUNTINGTON, Peter P., MD, New York
JONES, John E., MD, Texas
KEEFE, John F., MD, Massachusetts
KITZES, David L., MD, Rhode Island
LICHSTEIN, Edgar, MD, New York
*MALHOTRA, Jagdish C., MD, New York
MALOY, William C., MD, South Carolina
MARTIN, C. Edwin, MD, Pennsylvania
MARTINEZ-Pico, Amalia, MD, Puerto Rico
MARTINEZ-Rios, Marco A., MD, Mexico
MEHTA, Satchidanand, MD, Illinois
MEISNER, Marvin H., MD, Pennsylvania
MEYER, Jerry F., MD, District of Columbia
NACHNANI, Gurbux H., MD, Maryland
OLICHNEY, Michael J., MD, Virginia
QUOCK, Collin P., MD, California
RAMIREZ, Alberto, MD, Massachusetts
ROITMAN, David I., MD, Alabama
SAWAYAMA, Toshitami, MD, Japan
SCHRANK, Joel P., MD, Virginia
SCHWIMMER, Julius, MD, New York

Affiliate

APONTE-Lopez, Jose A., MD, Venezuela
BASU, Subrata K., MD, Connecticut
CANTOR, Herbert C., MD, Michigan
*CHAMBERS, James, MD, Iowa
CONTRERAS-Leon, Adolfo E., MD, Mexico
EPPARD, David A., MD, Massachusetts
GERSHENGORN, Kent N., MD, California
KERBER, Richard E., MD, Iowa
*LINARES-Cruz, Hector, MD, El Salvador
MONROE, Ralph C., MD, Massachusetts
MURGUIA-Suarez, Juan J., MD, Mexico
NORRIS, Jay, MD, New York
OLLIFF, Benjamin C., MD, Georgia
SANCHEZ-Nino, Pablo E., MD, Mexico
SCHLESINGER, Roberto, MD, Venezuela
SMITH, McKamy, MD, Alabama
SOLER-Planas, Mateo, MD, Mexico
STENLUND, Roger R., MD, Minnesota
URIBE-Longoria, Artemio, MD, Mexico

*Individuals who were elected to membership in the American College of Cardiology on August 10, 1971.

Personals

Dale Groom, MD, FACC, director, Oklahoma Regional Medical Program (**left**) and George Griffith, MD, FACC, senior cardiac consultant, Los Angeles, discuss cardiovascular problems at a recent taping of a continuing education television program for physicians, "Always on Tuesday," KETV, Oklahoma City, Okla.

PAUL N. YU, MD, FACC, has been named president-elect of the American Heart Association. Dr. Yu, who will be installed as AHA president next November, is Sarah McCort Ward Professor of Medicine and head of the Cardiology Unit at the University of Rochester Medical Center and a physician at the University's Strong Memorial Hospital, where the cardiology unit he directs includes the coronary care unit and the myocardial infarction research unit. He is also a consulting cardiologist at Genesee and Highland hospitals, Rochester; the Veterans Administration Hospital, Bath; the Newark-Wayne Community Hospital, Newark, N. Y.; and the Frederick Thompson Hospital, Canandaigua, N. Y.

Obituaries

Our College, indeed our nation, has lost a great pioneer in medicine, a man who with ingenuity and with courage has left a deep imprint on medical history. He was a part of the very beginning of the ever accelerating medical progress of our own generation.

Claude Schaeffer Beck was born in Shamokin, Pa., November 8, 1894. He took his bachelor's degree at Franklin and Marshall College in 1916 and his MD degree at Johns Hopkins in 1921. Franklin and Marshall awarded him a DSc. in 1937. His work in cardiac surgery began when he was Cabot Fellow in research surgery at Harvard and associate surgeon at the Peter Bent Brigham Hospital in 1923 and 1924; the next year he went on to become Crile Fellow in surgery at Western Reserve in Cleveland.

Cleveland was the site of his subsequent career. He held various positions in Cleveland hospitals, specializing in surgery of the heart as attending surgeon and as consultant; he was one of the founders of the American Board of Thoracic Surgeons. For his aggressive pioneering work, especially in the Crile Veterans' Hospital, he was decorated with the Legion of Merit in 1945.

Claude was elected an Honorary Fellow of the College in 1955 and a Vice President in 1959. He was appointed chairman of the Committee on Resuscitation by George Meneely and reap-

Dr. Beck

pointed by Louis Bishop. Claude kept pressing for instruction in cardiac resuscitation. The first on the scene in an emergency are always the ambulance, the police and fireman rescue crews, and they must be taught what and how to do when minutes count. A quarter of a century ago Claude Beck saw the need for training laymen to be medical assistants, a program that is a current idea in today's academia. In 1950 he started the courses; 2 days out of each month he turned his research laboratory at Western Reserve University into a classroom with actual demonstration on live dogs to groups of medical and nonmedical students. In New York City the work was carried on by our own Paluel Flagg assisted by Robert Hosler, one of Beck's associates. Our College was involved and our Journal carried articles contributed by the Resuscitation Committee.

By 1958 the record shows that almost 2,000 people had taken these courses in monthly groups of about 20. Beck kept records of patients who had been brought back to life; they had reunion meetings and took group pictures, "graduates of the mortuary."

A dramatic event was a country-wide closed circuit television program on November 13, 1957, "Grand Rounds," watched by 30,000 doctors. Reports were beamed from London; Paul White made an address from Italy. Our Charles Bailey performed an endarterectomy before the cameras in Philadelphia, and in Cleveland Claude and his research team did a "Beck 1" revascularization procedure, sprinkling sterile asbestos powder directly on to the heart muscle. Both of these procedures were "firsts," performed by Fellows of the College for all the medical world to see.

Last year, in Cleveland, Claude Beck, at age 75, suffered a stroke. This year on October 14, shortly before what would have been his 77th birthday, he died. For such a dynamic individual it is pleasant to remember that he was a compassionate and kindly person, a good friend, modest in accepting the honors that came to him, and to the end a loyal Fellow of the College.

PHILIP REICHERT, MD, FACC
ACC Historian

BURR C. BOSTON, MD, Waterloo, Iowa, was born in that city February 1, 1899, and died June 18, 1971. He was a graduate of Iowa State University and received his MD degree from the University of Chicago. He began medical practice in Waterloo in 1928 and retired April 1, 1971. He was a member of the Blackhawk County and the Iowa Medical Societies and had been an affiliate of the American College of Cardiology since 1954. Dr. Boston is survived by his wife, who resides at 921 Fletcher, Waterloo, Iowa.

DONALD L. WARKENTIN, MD, FACC
ACC Governor for Iowa

SAMUEL G. SHEPHERD, MD, FACC, Philadelphia, Pa., was born in Philadelphia on July 4, 1880, and died on September 10, 1971. He was educated in Philadelphia and was graduated from the Medico Chirurgical College of Philadelphia, Department of Pharmacy in 1900, and from the Medico Chirurgical Medical College in 1903.

Dr. Shepherd was a member of many hospital staffs during his medical career, among them, the Harvard University Hospital, Methodist Hospital, Jefferson Hospital, Graduate Hospital, and the Presbyterian Hospital. Dr. Shepherd received postgraduate training from 1930 until 1945 at the University of Penna., Harvard University, Johns Hopkins Hospital, University of Maryland, University of Minnesota, New York University, Columbia University, and the Philadelphia General Hospital. At the time of his death, he was physician emeritus of the Presbyterian-University of Pennsylvania Medical Center.

Dr. Shepherd was a member of the Philadelphia County Medical Society, the Pennsylvania State Medical Society, the American Medical Association, Philadelphia College of Physicians, International Society of Internal Medicine, Pathology Society and Pediatrics Society. He was past director of the Medical Club of Philadelphia and past president of the Aesculapian Club, and a member of the "50 Year Club of American Medicine." He was a Fellow of the American College of Physicians and had been a Fellow of the American College of Cardiology since 1951.

Dr. Shepherd is survived by his widow, Mrs. Jeanette Adler Shepherd, 301 S. 19th St., Philadelphia, Pa.

SAMUEL BELLET, MD, FACC*
ACC Governor for Eastern Pennsylvania

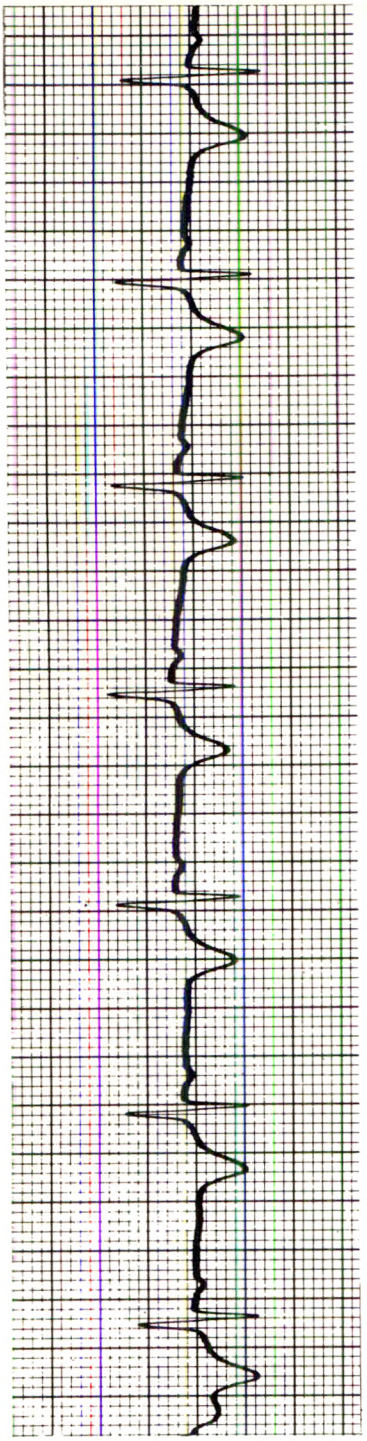
HERBERT UNTERBERGER, MD, FACC, Drexel Hill, Pa., was born in Wilkes Barre, Pa. on June 13, 1920 and died on April 5, 1971. He obtained his MD degree from the Jefferson Medical College in 1945. In addition, he obtained a MSc degree in internal medicine from the University of Pennsylvania in 1951. He was a graduate student in internal medicine from 1948 to 1949 at the University of Pennsylvania, a Fellow in internal medicine from 1949 to 1951 and a Fellow in Cardiology from 1951 to 1952 at the Woman's Medical College Hospital of Philadelphia.

Dr. Unterberger was associate professor of medicine at the Woman's Medical College of Philadelphia; director of medicine of the Haverford State Hospital; chief of medicine, Haverford Hospital; assistant chief of medicine, Philadelphia General Hospital; attending physician, Veterans Administration Hospital; attending physician and chief of medicine of the Delaware County Memorial Hospital; and chief of cardiology, Valley Forge General Hospital. Dr. Unterberger was a member of the American Medical Association, American Heart Association and a Fellow of the American College of Physicians. He had been a Fellow of the American College of Cardiology since 1963.

He is survived by his wife, Mrs. Cherie Unterberger, 271 Wiltshire Rd., Philadelphia, Pa. 19151.

SAMUEL BELLET, MD, FACC*
ACC Governor for
Eastern Pennsylvania

* Dr. Bellet died on December 13, 1971.



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Bernard Lown, M.D. and Suzanne B. Knoebel, M.D.

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Book Review
E. Grey Dimond, M.D.

Scanning the Literature
E. Grey Dimond, M.D.

Side 2

Management of Combined Cardiac and Pulmonary Failure
A Panel Discussion—Gerald Baum, M.D. and Myron Stein, M.D. Moderated by Alfred Soffer, M.D.

Are Cardiovascular Deaths Caused by Some Broncho-dilators Secondary to the Propellant or the Medication?
Israel Bruderman, M.D. and Alfred Soffer, M.D.

Scanning the Literature
E. Grey Dimond, M.D.

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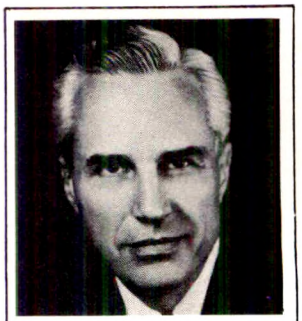

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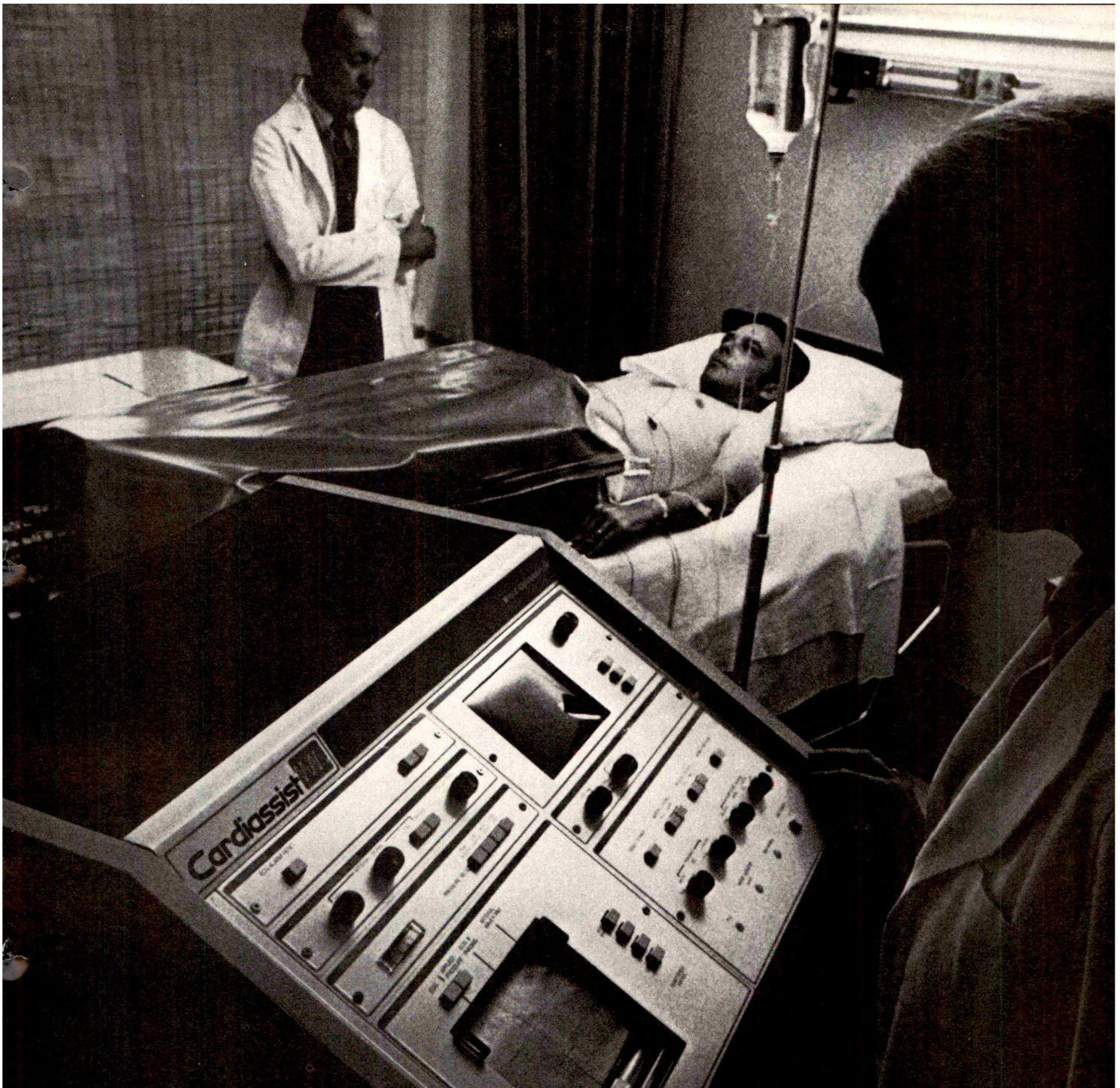

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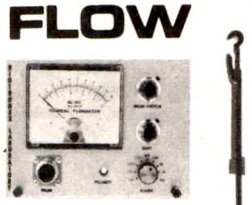

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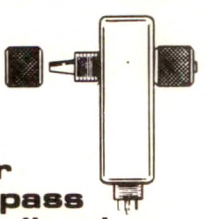

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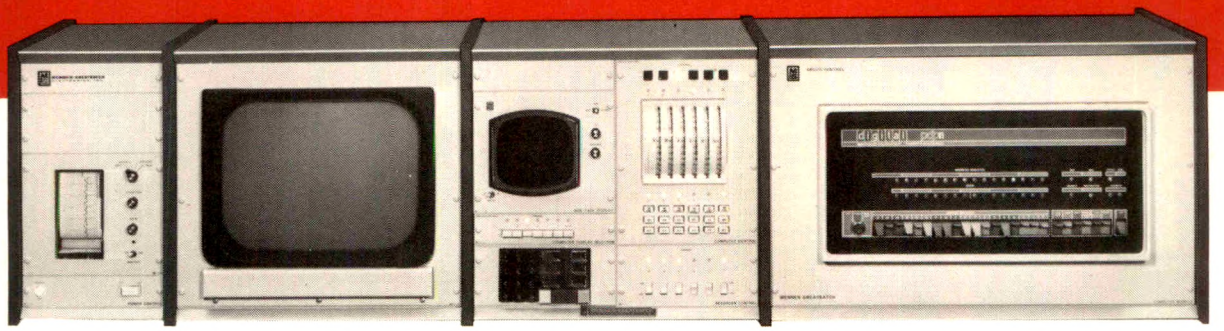

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*Based on the work of the Biomedical Computer Laboratory and the Department of Medicine of the Washington University School of Medicine and the Coronary Care Center of Barnes Hospital, St. Louis, Missouri.

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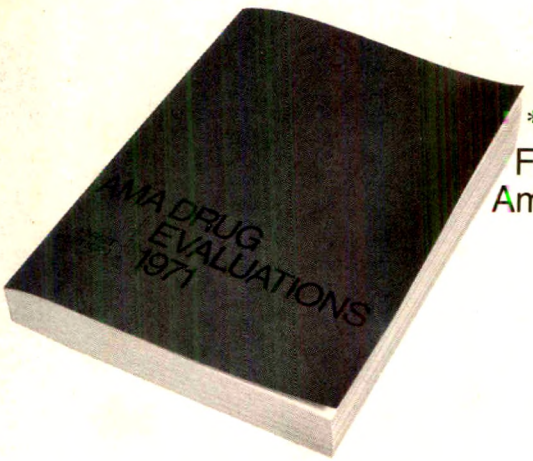
"The drug of choice for oral replacement of potassium is potassium chloride solution."*



*AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

19 FEB 1973

Kay Ciel® Elixir is potassium chloride ...and it tastes good, too!

Composition: Each 15 cc. (one tablespoonful) contains potassium chloride 1.5 Gm., supplying 20 mEq. of elemental potassium, in a cherry-flavored, palatable base, alcohol 4%. Contains no sugar.
Indications: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium or as a result of excessive vomiting and diarrhea.
Contraindications: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
Precautions: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
Side Effects: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
Dosage and Administration: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
How Supplied: One pint and one gallon bottles.

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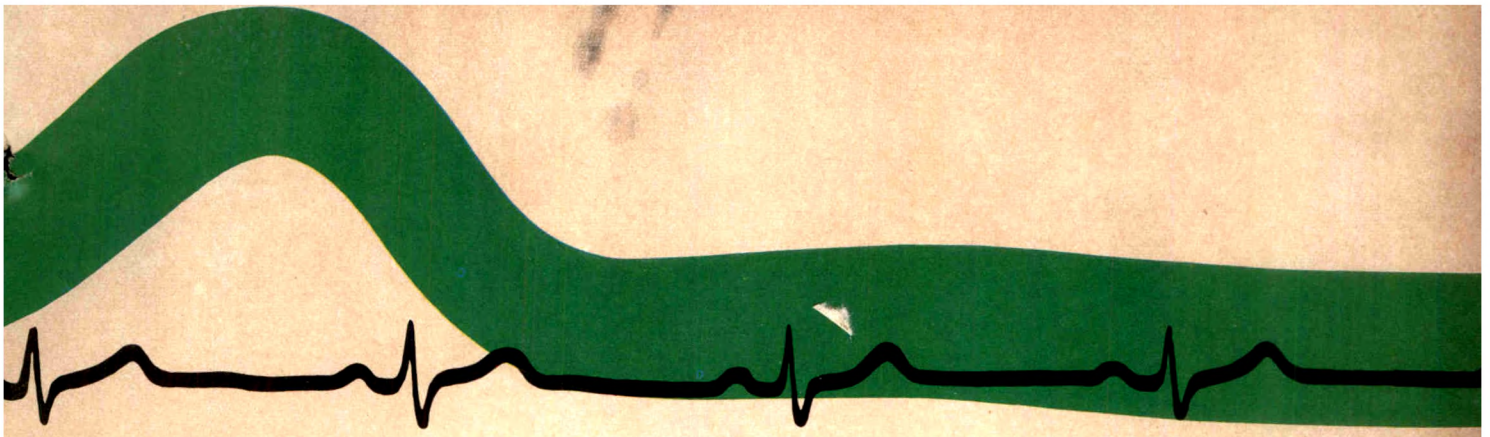

when quinidine is indicated

for maintaining normal sinus rhythm
following conversion by other techniques

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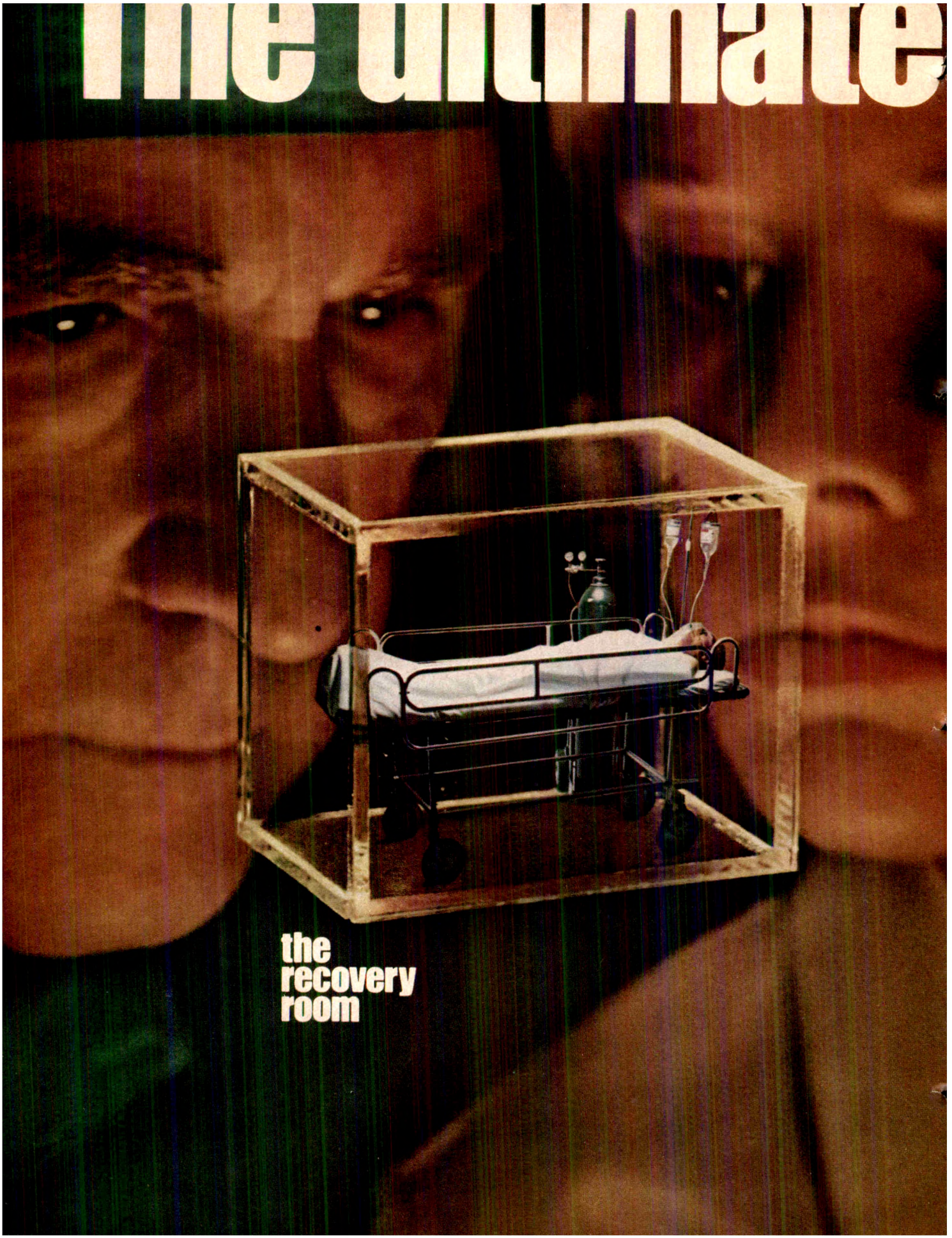
Quinaglute maintenance—what it means to you night... and day

- prolonged control without peaks and valleys
- helps prevent premature ventricular contractions in the early morning hours
- helps prevent early morning reversion in atrial fibrillation after normal sinus rhythm has been established by other techniques

Indications: For the prevention of premature atrial, nodal or ventricular contractions. For maintenance of normal sinus rhythm following conversion by other techniques of atrial, nodal or ventricular tachycardia, atrial flutter and fibrillation (paroxysmal or chronic).
Contraindications: Same as for other forms of quinidine, including partial A-V or complete heart block; intraventricular conduction defects, especially marked QRS widening; sensitivity to quinidine; renal disease with significant azotemia; development of cardiotoxic effects (conduction defects or ventricular premature beats, ventricular tachycardia, or flutter) while taking the drug; marked cardiac enlargement with congestive failure; poor renal function especially with tubular acidosis.
Precautions: Same as for quinidine. To detect idiosyncrasy, e.g., febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment, administer preliminary test dose of single tablet of quinidine sulfate. Use extreme caution in patients with severe heart disease, congestive heart failure, digitalis intoxication, renal insufficiency. Administer cautiously, if at all, to senile patients. Hospitalization (for close observation, ECG monitoring and possibly plasma quinidine levels) indicated when administering large doses with patients presenting increased risk. With the dosage regimen (see "Dosage") of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythms. Should not be used during pregnancy.
Adverse reactions: Instruct patients to report any symptoms of cinchonism at once (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, and respiratory distress); the drug should be discontinued immediately if such symptoms or evidence of hypotension occur. If gastrointestinal disturbances (rarely reported) occur, they may be minimized by administering the drug with food, or if they persist, dosage shoud be decreased.
Dosage: The dosage varies considerably depending upon the general condition and cardiovascular state of the patient. The quantity and frequency of administration must be determined for each patient. For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours. For maintenance of normal sinus rhythm following conversion by other techniques of atrial fibrillation, tachycardia or flutter, 2 tablets every 12 hours or 1½-2 tablets every 8 hours are usually required. The occasional patient may be maintained in normal rhythm on a dosage of 1 tablet every 12 or 8 hours. Occasionally larger or more frequent dosage may be required, but such increases should be used only after thorough evaluation of the patient, including serial electrocardiograms and determination of plasma quinidine levels. The ideal dosage is the minimum amount of total dose and frequency of daily administration that will prevent premature contractions, paroxysmal tachycardias, and maintain normal sinus rhythm. **Supplied:** Bottles of 100 and 250 tablets.

Cooper Cooper Laboratories, Inc., Wayne, N.J. 07470, U.S.A. Ste. Therese, P.Q., Canada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the recovery room

test: confirms the value of Talwin in the hospital

analgesic efficacy comparable to meperidine and morphine with a *minimum* of significant adverse effects

In postoperative patients: less circulatory depression with Talwin

In a double-blind study of 342 postop patients, circulatory depression occurred in 13.2% of 174 patients receiving morphine; in 5.4% of 168 patients receiving Talwin.[1]

. . . and in other patients: less respiratory and circulatory depression with Talwin

In a double-blind study of 3 narcotic analgesics and Talwin in 118* patients with suspected acute myocardial infarction, Talwin caused a significantly lower incidence in the fall of systolic blood pressure than the 3 narcotics when the initial pressure was 120 mm. Hg or higher. Unlike the narcotics, Talwin caused a statistically significant *rise* in the systolic blood pressure of patients with initial pressures of less than 120.[2]

In a study of a series of patients given Talwin or meperidine while anesthetized for surgery, the investigators concluded: "It would therefore appear that pentazocine is a much safer drug in respect of respiratory depression than pethidine [meperidine], particularly when repeated injections are to be given, e.g., postoperatively or in obstetric practice."[3]

. . . and less of other adverse effects associated with narcotic analgesics

Compared to morphine, Talwin is relatively free from urinary retention and constipation.

Is less likely to cause nausea, vomiting and diaphoresis than meperidine.

See next page for a complete discussion of adverse reactions and a brief summary of other Prescribing Information.

available in 3 dosage strengths—all within the range of recommended dosage
Talwin is available in 30 mg., 45 mg., and 60 mg. strengths to provide analgesia specific to patients' needs throughout the course of therapy. Most studies indicate that the higher dosage strengths produce little, if any, increase in the incidence of adverse reactions.

References: 1. Wallace, George: *Int. Surg. 53*:135, Feb. 1970.
2. Scott, M. E. and Orr, Rosemary: *Lancet 1*:1065, May 31, 1969.
3. Davie, I. *et al.*: *Brit. J. Anaesth. 42*:113, Feb. 1970.

*Other drugs studied: diamorphine and methadone.

Injectable
Talwin®
Brand of
pentazocine
(as lactate)

bulwark against moderate to severe pain

been observed
• not subject to narcotic controls

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor. Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, nodules and ulceration at injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

Patients in Labor. The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.),* each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. Boxes of 10, 25, and 100.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide.

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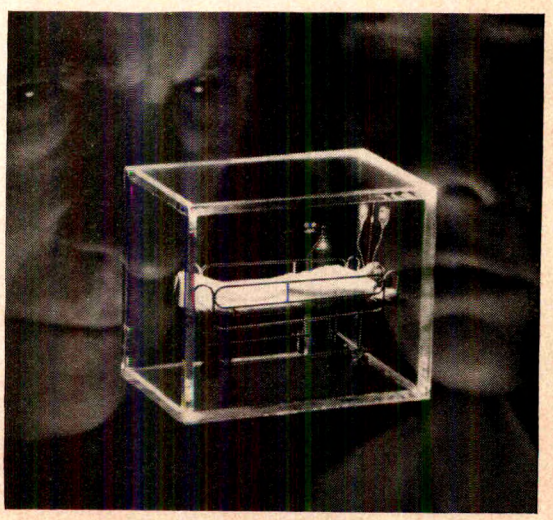

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in the hospital

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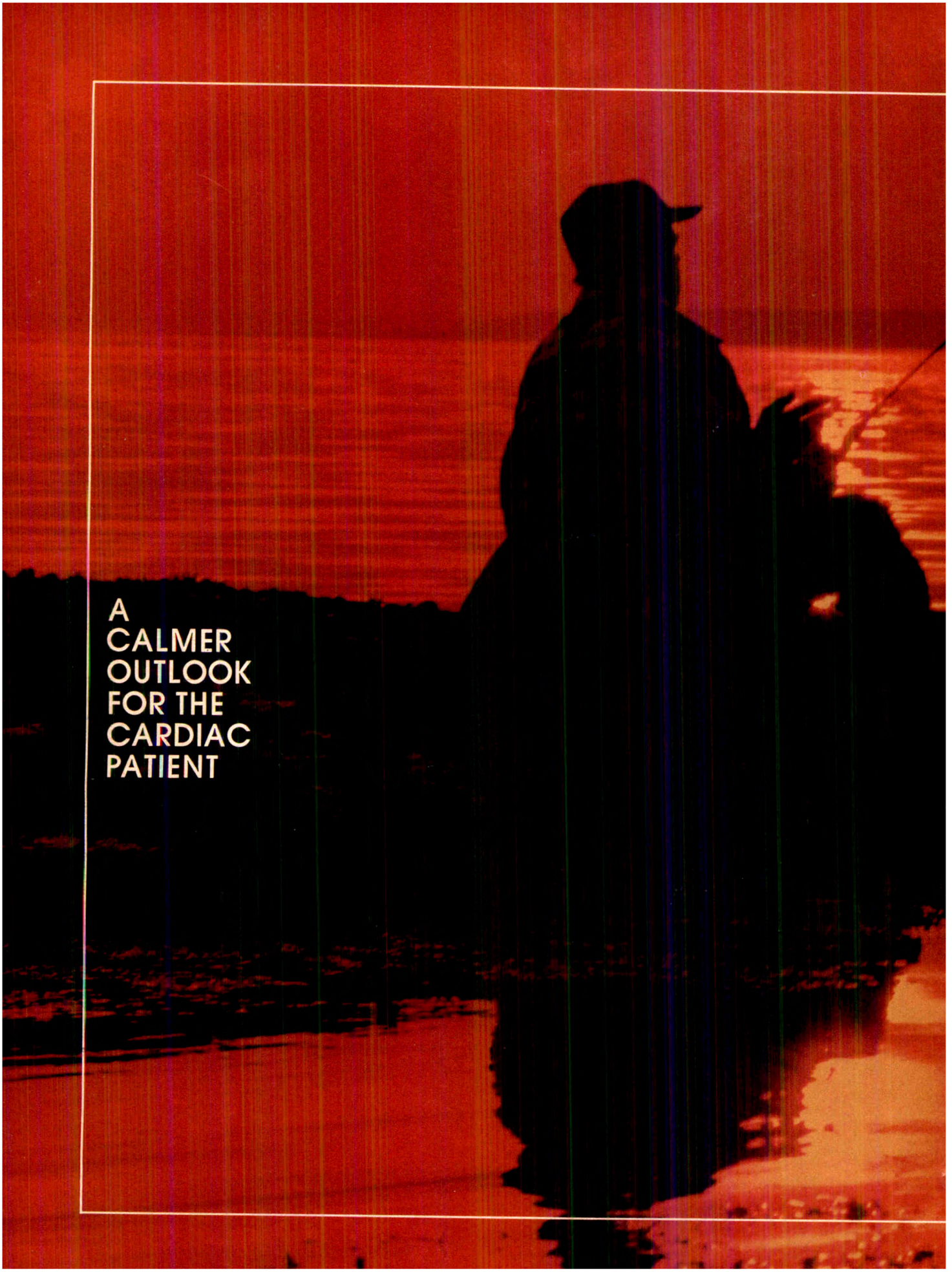
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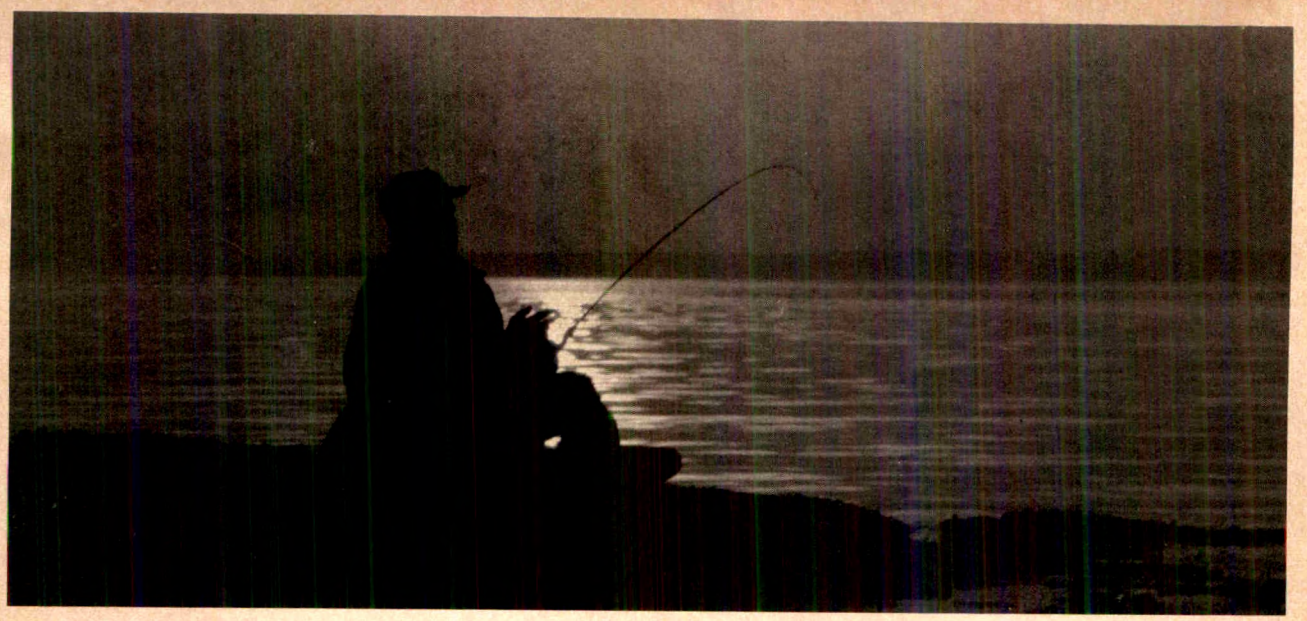
Please see Brief Summary on next page for further discussion of side effects and contraindications.



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BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use must not be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./cc.—10 cc. vial; 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit; 100 mg./2 cc. unit.

More detailed professional information available on request.

Revised January, 1970

Pfizer **LABORATORIES DIVISION**
PFIZER INC., NEW YORK, N.Y. 10017

The American Journal of CARDIOLOGY

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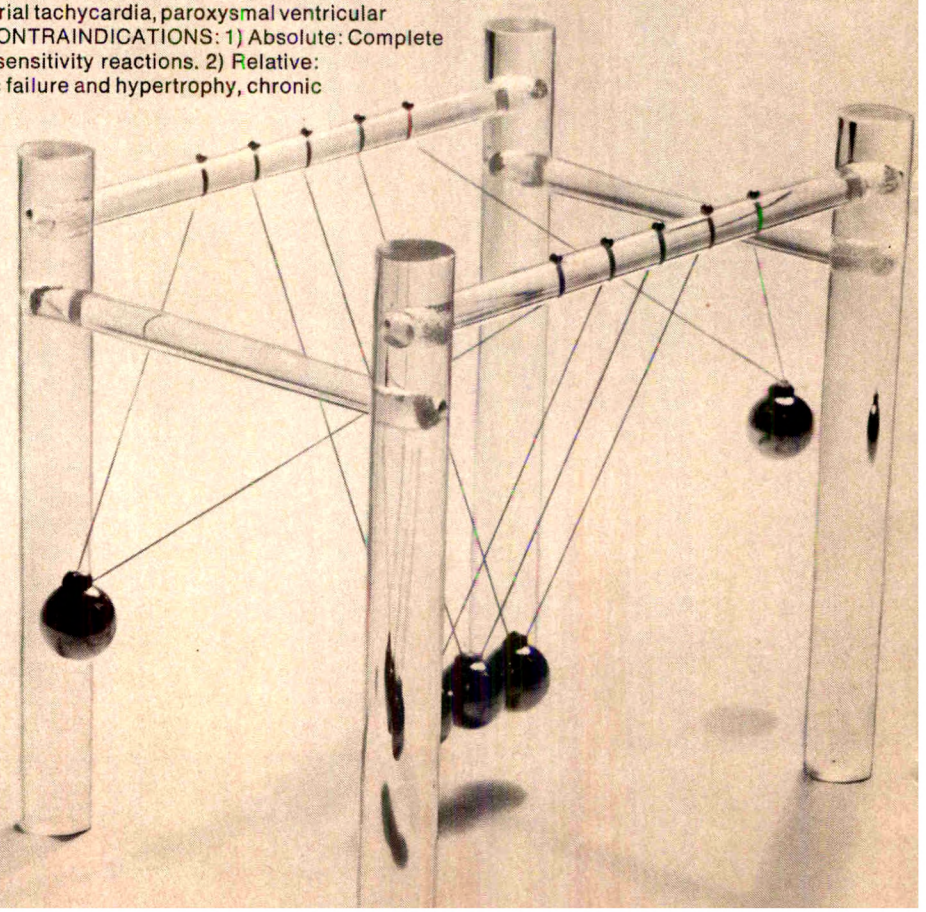

Alone among antiarrhythmics...

MARCH 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 3

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CLINICAL STUDIES

315 **Circulatory Effects of Practolol**

ROBERT E. FINEGAN, ANTHONY M. MARLON and DONALD C. HARRISON

This study of the hemodynamic effects of practolol, a relatively selective beta adrenergic blocking agent with more negative chronotropic than negative inotropic effects, demonstrates that this drug used in appropriate doses in patients with heart disease produces competitive beta blockade without concomitant deterioration of ventricular function. In low doses the drug appeared to augment the contractile state of the heart.

323 **Evaluation of Left Ventricular Function from Isovolumic Pressure Measurements During Isometric Exercise**

HANS PETER KRAYENBUEHL, WILHELM RUTISHAUSER, MANFRED SCHOENBECK and IVO AMENDE

During handgrip left ventricular systolic pressure, end-diastolic pressure and heart rate increased significantly in 2 groups of patients undergoing diagnostic cardiac catheterization; group 1, 13 patients without or with minimal loading of the left ventricle, and group 2, 11 patients with a primarily pressure-loaded left ventricle or coronary heart disease. The increase in left ventricular end-diastolic pressure, was far greater in group 2. It is concluded that the primary response of the normal or near normal left ventricular myocardium to an acute load produced by handgrip is an enhancement of the contractile state, whereas the compromised left ventricular myocardium characteristic of patients in group 2 probably utilizes the Frank-Starling mechanism to generate increased pressure.

331 **Cardiac Arrhythmias Observed During Maximal Treadmill Exercise Testing in Clinically Normal Men**

PAUL L. McHENRY, CHARLES FISCH, JOHN W. JORDAN and BETTY R. CORYA

This study of 650 men aged 25 to 54 years demonstrates that arrhythmias, usually transient and in the form of unifocal ventricular or supraventricular premature contractions, are quite common during strenuous exercise testing in men without clinical evidence of heart disease. Patients with definite or suspected cardiovascular disease experience a greater incidence of frequent ventricular premature contractions, multifocal ventricular premature beats and ventricular tachycardia. The appearance of unifocal ventricular premature contractions during maximal or near maximal exercise testing does not indicate clinically significant cardiac disease.

337 **The QRS Loop in Left Anterior and Posterior Hemiblocks. Vectorcardiographic Study During Selective Coronary Arteriography**

FRANCISCO FERNÁNDEZ, JOSEPH HELLER, GIAM-PAOLO TREVI, SERGE RABENOU, LUCIEN SCEBAT and JEAN LENÈGRE

Selective coronary arteriography in 26 patients induced transient left intraventricular hemiblocks which were studied vectorcardiographically. Changes in the QRS loops and terminal QRS vectors are described. These help to clarify the changes occurring in cases of marked left axis deviation, "periinfarction block" and left or right bundle branch block with QRS axis deviation.

continued

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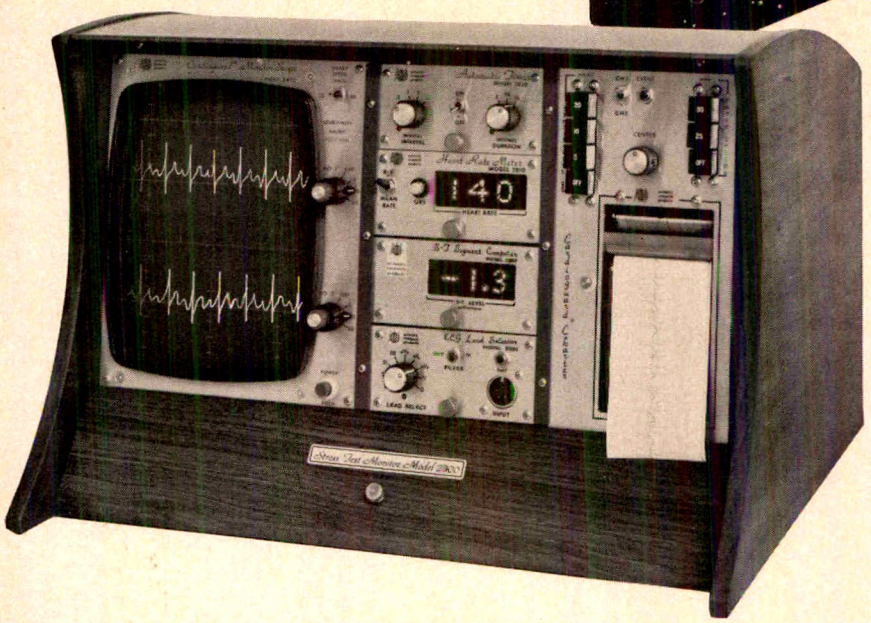

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344 The Incidence and Mortality of Intraventricular Conduction Defects in Acute Myocardial Infarction

JACQUES J. COL and SYLVAN L. WEINBERG

Intraventricular conduction defects during sinus mechanisms developed in 24 percent of 212 consecutive cases of acute myocardial infarction observed in a coronary care unit. Patients with these defects (QRS prolongation, incomplete bilateral bundle branch block) had a higher mean age and greater mortality (47 percent) than for the entire series. Left anterior hemiblock, the most innocuous defect observed, occurred in 9.4 percent of the patients and resulted in an in-hospital mortality rate of 25 percent, which was statistically not different from the mortality rate in the entire series.

351 Aberrancy of Junctional Escape Beats. Evidence for Origin in the Fascicles of the Left Bundle Branch

RASHID A. MASSUMI, GUNGOR E. ERTEM and ZAKAUDDIN VERA

This study of the aberrancy of so-called atrioventricular junctional escape beats in 5 patients using His bundle electrography in 3, establishes the escape focus in 1 of the 2 fascicles of the left bundle branch. Beats displaying right axis deviation arise in the superior division; those with left axis deviation arise in the inferior division. There is bidirectional propagation of escape beats simultaneously toward the ventricular myocardium and retrograde toward the main His bundle.

360 The Preoperative and Operative Assessment of Aortic Regurgitation. Cineaortography vs. Electromagnetic Flowmeter

ROBERT G. MENNEL, CLAUDE R. JOYNER, Jr., PAUL D. THOMPSON, RICHARD R. PYLE and HORACE MACVAUGH III

Quantitative measurement of aortic regurgitant blood flow by the use of a sine wave electromagnetic flowmeter applied to the ascending aorta of 25 patients during thoracotomy reveals that the severity of aortic regurgitation may differ greatly from that estimated preoperatively by supravalvular cineaortography. A more reliable method than supravalvular cineaortography is required for the accurate preoperative assessment of the hemodynamic severity of aortic regurgitation.

EXPERIMENTAL STUDIES

367 The Subendocardial Lymphatics of the Canine Heart. A Possible Role of the Lymphatics in the Genesis of Conduction Disturbances and Arrhythmias

HERMAN N. UHLEY, SANFORD E. LEEDS, MARY ANNA SUNG with the technical assistance of SHANTILAL PATEL and ENRIQUE LOBOS

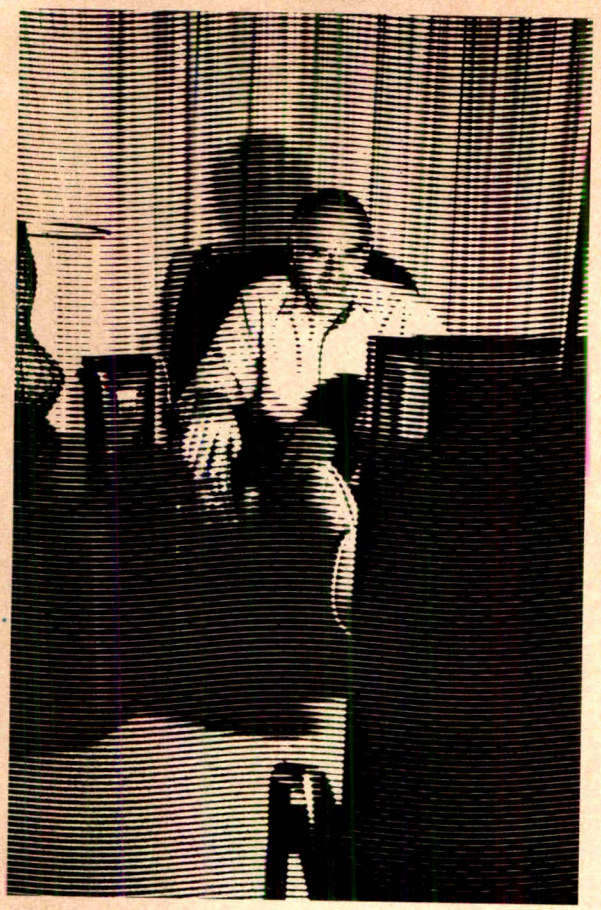
The subendocardial lymphatics of the canine right ventricle traverse the main right bundle at many levels and intersect with longitudinal lymphatics following the course of the bundle. It is suggested that the lymphatics may play a role in pathologic lesions involving the conduction system, either by direct involvement, or indirectly by carrying a large concentration of potassium from remote damaged areas. The potassium effect may be manifested by a conduction defect or development of arrhythmias.

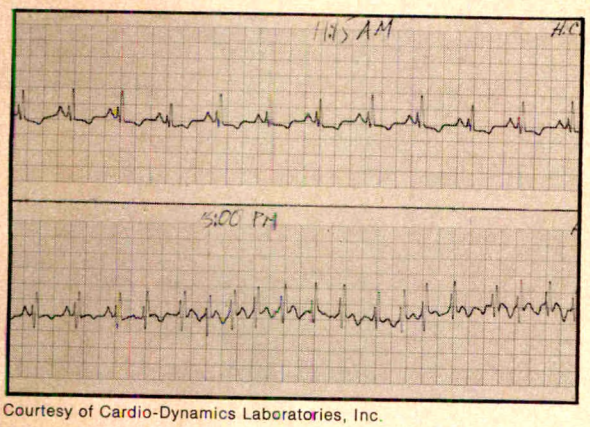
372 Electrical Properties of the Thoracic Veins

DOUGLAS P. ZIPES and RUSSELL F. KNOPE

This preliminary study in dogs demonstrates that electrical stimuli delivered to the venae cavae and the azygos and pulmonary veins conduct to the atrium with electrical properties similar to those of atrial muscle. It is quite likely that atrial muscle extends for a distance into these veins.

Holter DCG Monitoring Case History No.15





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A 53-year-old male physician with a history of coronary artery disease had symptoms consistent with a recurrent tachyarrhythmia which was not confirmed by routine electrocardiography. Therefore, the attending physician ordered a continuous, 12-hour dynamic electrocardiogram (DCG).

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377 Magnesium Sulfate in Digitalis Toxicity

MARTIN S. NEFF, SAUL MENDELSSOHN, KWAN E. KIM, STANLEY BANACH, CHARLES SWARTZ and ROBERT H. SELLER

This dog study demonstrates that a high level of magnesium concentration may overcome the acetyl strophanthidin-induced inhibition of transport adenosine triphosphatase. This action may explain the value of magnesium sulfate in the treatment of digitoxic arrhythmias associated with hypomagnesemia. The data also suggest that factors independent of potassium loss from the myocardium also underlie the development of some digitoxic arrhythmias since arrhythmias occurred in 60 percent of the animals despite blocking of potassium egress from the myocardium.

METHODS

383 Clinical Studies with a Solid State Fiberoptic Oximeter

JAMES S. COLE, WAYNE E. MARTIN, PETER W. CHEUNG and CURTIS C. JOHNSON

The capacity of this new fiberoptic catheter oximeter to measure oxygen saturation and pressure continuously for 72 hours without withdrawal of blood samples or heparinization of the patient makes it useful in selected critically ill subjects. Special precautions to prevent destruction of the fibers, some problems with catheter size, blood clot formation on the catheter and limitations in interpretation of data are discussed.

389 Reliability and Normal Variations of Computer Analysis of Frank Electrocardiogram by Smith-Hyde Program (1968 Version)

ROBERT A. BRUCE, STEPHEN R. YARNALL with the assistance of ROBERT STRATBUCKER, GLADYS PETTIT, VERONA HOFER and DONOVAN J. THOMPSON

The computer analysis of the Frank X, Y and Z leads using the Smith-Hyde analytical program in 334 healthy persons and 39 patients with heart disease provided an overall sensitivity of 76 percent for true positives (abnormal electrocardiograms) and specificity of 75 percent for true negatives (normal electrocardiograms) for the perdominantly normal case material used in this study. These results indicate a need for continuous surveillance of all records by a cardiologist to assure quality control and to avoid the risk of "computerogenic heart disease" and anxiety of a patient.

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397 Effect of Sotalol on Clinical Arrhythmias

RAVI PRAKASH, WILLIAM W. PARMLEY, HOWARD N. ALLEN and JACK M. MATLOFF

In clinical testing, Sotalol, a new beta adrenergic blocking agent, proved efficacious in terminating, preventing or controlling 22 episodes of supraventricular and 6 episodes of ventricular tachycardia in 20 patients. This drug appears to be a moderately effective antiarrhythmic drug; its lack of substantial myocardial depressant effects may make it preferable in some conditions to other beta adrenergic blocking agents. Side effects requiring a reduced dose included transient hypotension in 3 patients and bradycardia in 4.

SEMINAR ON CLINICAL APPLICATION OF TECHNIQUES TO MEASURE BLOOD FLOW IN MAN. PART III

401 Velocity and Flow Measurements by Electromagnetic Techniques

PAUL D. STEIN

This review of electromagnetic flowmetry emphasizes the cardiovascular applications of velocity and flow measurements in patients and discusses a variety of electromagnetic catheter tip devices and their potential applicability to patient care.

continued

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CASE REPORTS

408 Asymptomatic Rapid Ectopic Tachycardia Induced by and Persisting During Prolonged Exertion

HAROLD L. RUTENBERG and LOUIS A. SOLOFF

This case report illustrates the therapeutic dilemma not only of the physician but also of this 39 year old healthy patient with paroxysmal prolonged ventricular or atrioventricular junctional tachycardia at a rate of 214 beats/min during strenuous exertion in the upright position. The cause of this arrhythmia is uncertain.

412 Congenital Complete Atrioventricular Heart Block. A 25 Year Follow-Up Study

ROBERT A. CORNE and FRANCIS A. L. MATHEWSON

Experience with this 48 year old pilot with congenital complete heart block followed up for 25 years supports the impression of an excellent prognosis for this condition, provided there is no associated congenital structural heart disease. The QRS complexes are supraventricular in configuration, and the disorder is not familial.

416 Factors Influencing Longevity in Adults with Congenital Complete Heart Block

MALCOLM M. McHENRY

Only 3 of 8 adult patients with presumably congenital complete heart block remain without important symptoms, thus indicating that this condition is not benign and may rival acquired heart block in complications. Those with symptoms required permanent pacemakers. Further study suggests that these patients may have not only an anatomic disturbance of conduction but also depression of impulse formation in a low junctional pacemaker. Impaired autonomic activity appears to progress with age and is manifested by a failure to respond to intravenously administered atropine and by a reduced sympathetic response of heart rate to effort.

422 Aneurysm of the Nonpatent Ductus Arteriosus

M. WAYNE FALCONE, JOSEPH K. PERLOFF and WILLIAM C. ROBERTS

As in this illustrative case, about two thirds of aneurysms of the nonpatent ductus arteriosus occur in infants less than 2 months old. Operative resection appears to be indicated because rupture, embolism, infection or other complications tend to develop in almost half of the patients with this condition.

DIAGNOSTIC SHELF

427 Respiratory Variation of Left Ventricular Ejection Time in Patients with Pericardial Effusion

WILLIAM H. CARTER, HENRY D. McINTOSH and EDWARD S. ORGAIN

Left ventricular ejection times measured by external carotid pulse tracing in 2 patients with pericardial effusion and at most only an equivocal paradoxical pulse showed a 50 msec variation during respiration at a constant heart rate. Respiratory variation of left ventricular ejection time in control subjects was only 10 msec.

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JOHN C. KRANTZ, Jr.

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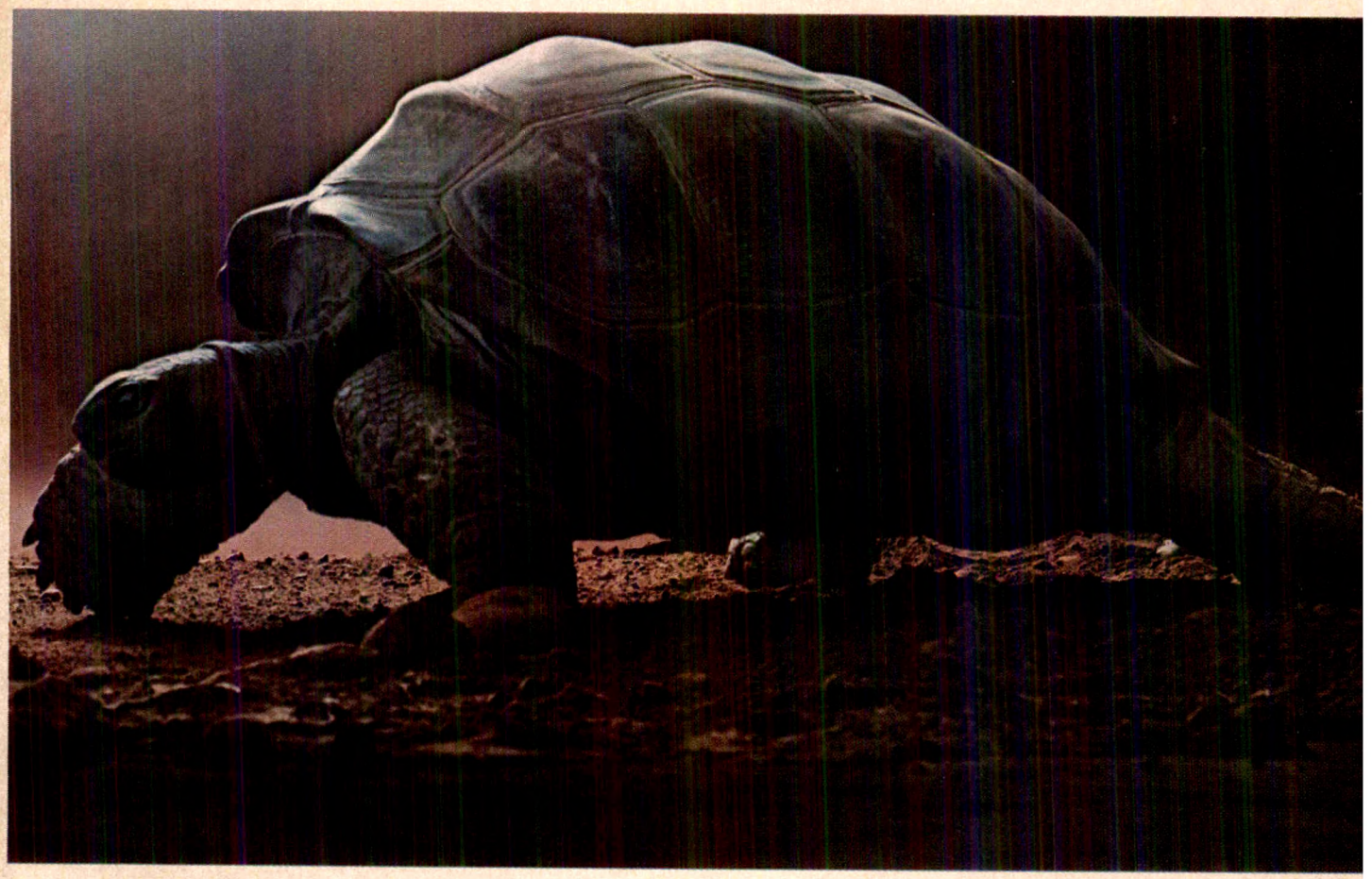

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Hygroton. 100 mg. tablets. Once daily.

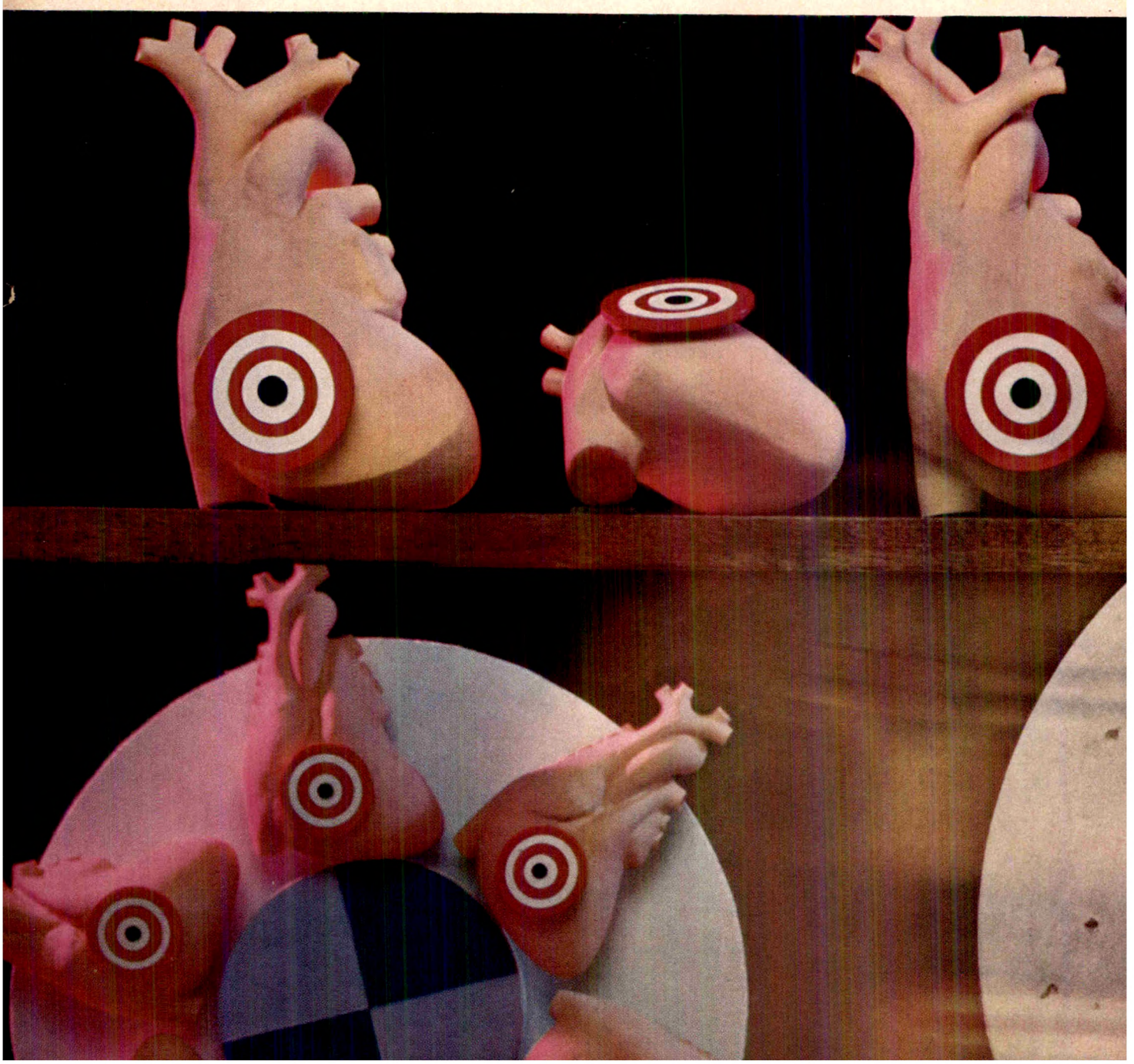
BRIEF SUMMARY

Indications: Edema, hypertension. **Contraindications:** Hypersensitivity and most cases of severe renal or hepatic diseases. **Warnings:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has been required frequently and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Use with caution in pregnant women and nursing mothers since the drug crosses the placental barrier and appears in cord blood and since thiazides appear in breast milk. The drug may result in fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. When used in women of childbearing age, balance benefits of drug against possible hazards to fetus. **Precautions:** Antihypertensive therapy with this drug should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Because of the possibility of progression of renal damage, periodic determination of the BUN is indicated. Discontinue chlorthalidone if the BUN rises or liver dysfunction is aggravated (hepatic coma may be precipitated). Electrolyte imbalance with sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, the drug should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. **Adverse Reactions:** Anorexia, nausea, vomiting, gastric irritation, cramping, constipation, headache, dizziness, weakness, restlessness, transient myopia, muscle cramps, dysuria, impotence, orthostatic hypotension (which may be potentiated by alcohol, barbiturates or narcotics); rare idiosyncratic reactions such as aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, necrotizing angiitis; allergic skin rashes, urticaria or purpura; hyperglycemia and glycosuria (diabetics should be checked regularly); hyperuricemia and acute gout; and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization. **Usual Dose:** One tablet daily. **How Supplied:** Tablets–100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000.

Hygroton® 100 mg.
(chlorthalidone USP)

The Ischemic Heart: Target for Ventricular Arrhythmias

While premature ventricular contractions (PVCs) are probably innocuous in most people without organic heart disease, they can be considerably more dangerous in middle-aged and elderly patients with myocardial ischemia. The incidence of death due to arrhythmia is substantially higher among such individuals, and is generally brought on by



PVCs triggering deadly ventricular fibrillation.

PRONESTYL (Procainamide Hydrochloride) may be especially suitable for these high-risk patients because of its recognized effectiveness against ventricular arrhythmias. PRONESTYL is available in capsules as well as injectable form. The capsules permit maintenance therapy at home and in the hospital.

PRONESTYL controls PVCs and ventricular tachycardia after oral, I.M. or I.V.* administration. An oral regimen of one 0.5 Gm. capsule every 4 to 6 hours may be especially suitable for patients endangered by runs of PVCs.

*Administer I.V. only in extreme emergencies.

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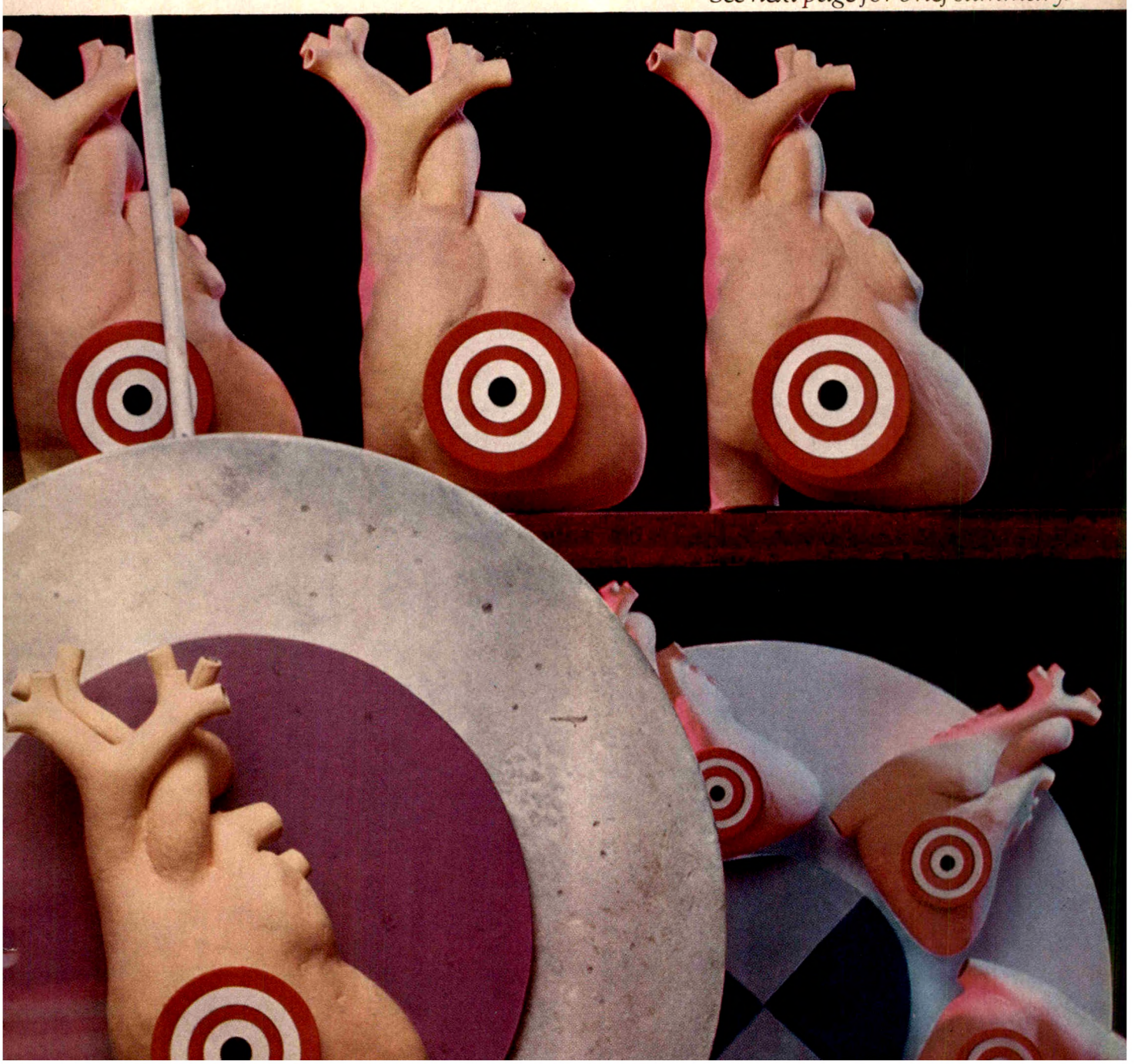
Pronestyl® (Procainamide Hydrochloride) zeroes in on ventricular arrhythmias

See next page for brief summary.



Pronestyl® (Procainamide Hydrochloride) Capsules & Injection zeroes in on ventricular arrhythmias

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 Gm. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. If any sign of lupus erythematosus occurs, LE cell tests should be performed; if cell tests are positive, discontinue drug. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide. Tests at regular intervals for lupus erythematosus are recommended for patients on maintenance therapy.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

Supply: Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 0.25 Gm. and 0.5 Gm. are available in bottles of 100 and 1000, and Unimatic® Single Dose Packaging in cartons of 100. Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) providing a 10% sterile aqueous solution (100 mg./cc.) with 0.9% (W/V) benzyl alcohol is available in 10 cc. vials. (A.H.F.S. 24:04) [Military FSN 6505-582-5370: Capsules, 0.25 Gm., 100's; FSN 6505-299-8614: Inj., 10 cc. vials; VA FSN 6505-582-5371A: Capsules, 0.25 Gm., 1000's.]

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A dramatic alternative in the clinical management of cardiogenic shock...

Cardiassist

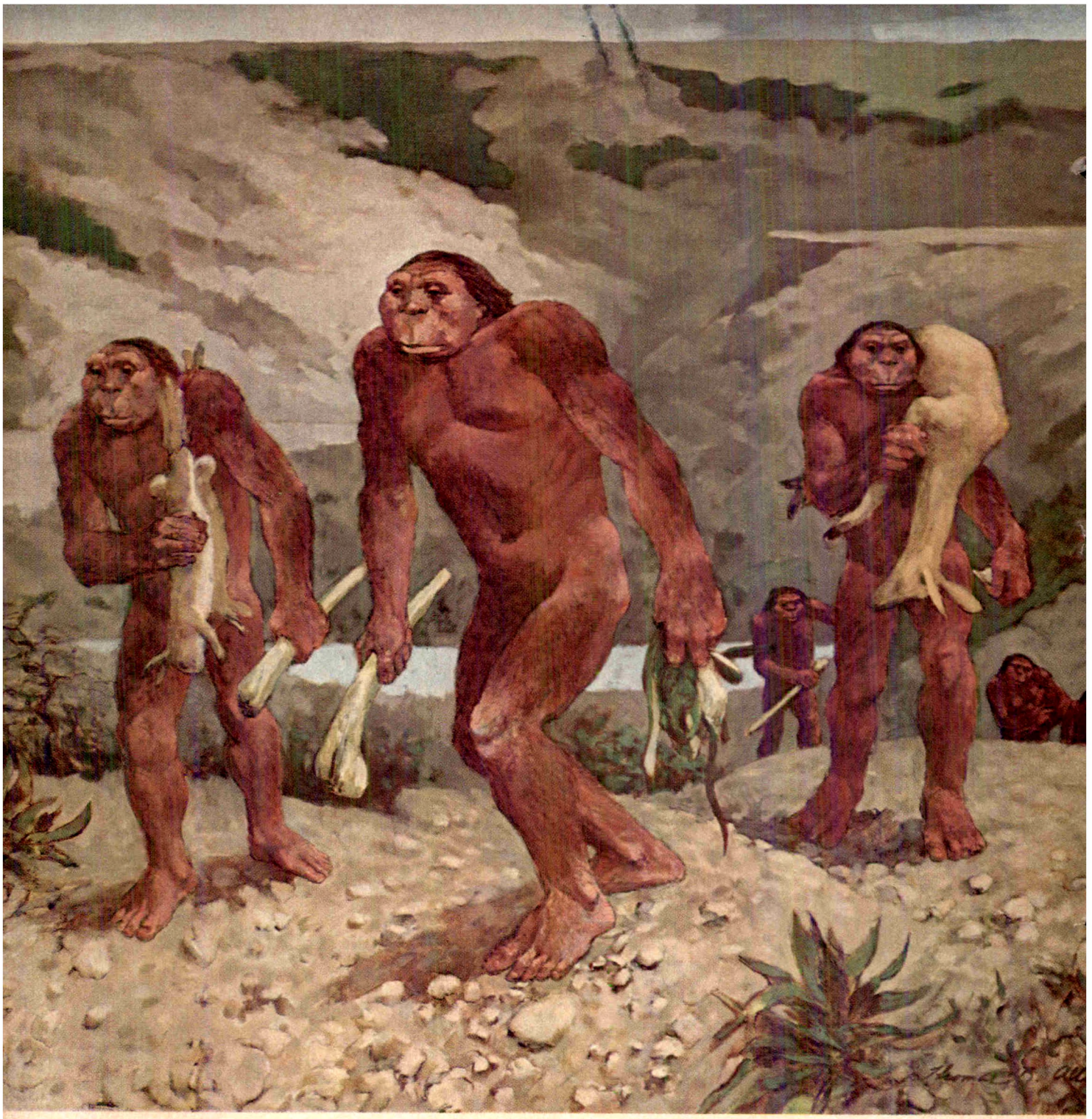
EXTERNAL PRESSURE CIRCULATORY ASSIST

CARDIASSIST is an external pressure circulatory assist device for producing counterpulsation to augment cardiac output, preferentially perfuse the myocardium and enhance perfusion of other vital organs in the treatment of myocardial ischemia and the management of cardiogenic shock. Unlike other earlier modalities of circulatory assist by counterpulsation, CARDIASSIST requires no surgical intervention or sterile procedures, no anesthesia or anticoagulants, and produces no measurable trauma. It is portable, quiet in operation, and can be applied in minutes, making it entirely compatible for use in emergency situations.

For more detailed information on the CARDIASSIST method of external pressure circulatory assist, write Medical Innovations, Inc., Dept. AJC , 69 Hickory Drive, Waltham, Mass. 02154. Telephone (617) 890-4266. Cable Address: MEDINCORP, Waltham, Mass. U.S.A.

Patents Pending

MEDICAL INNOVATIONS, INC.



Beginning of our hyperlipidemic way of life

One million years ago, a primitive ancestor of man assumed a meat-eating habit which he passed on to his descendants. According to Collens,[1] "... man has indulged himself in eating foods containing large amounts of cholesterol and saturated fats, although he does not have the anatomic and physiologic capabilities for handling these foods in a manner comparable to carnivores." As stated editorially in *Lancet*,[2] "the 'unnatural' diets of Western man are associated with a high proportion of saturated fatty acids in the blood...." Also, a large intake of carbohydrates cannot be overlooked as a contributory factor in hyperlipidemia.[2,3]

...today

One of five Americans over the age of seventeen has a serum cholesterol level of 260 mg./100 ml. or higher, according to the U.S. Public Health Service.* Stamler *et al.*[3] state: "A significant proportion of our population is frankly hypercholesterolemic." They further report that among the millions of adult Americans with this condition, a majority are entirely unaware of its presence because they have never been tested for it.

*Based on mean averages obtained by examining 6,670 persons out of a sample of 7,700. This group represented 111 million adults in the target population. Adapted from U.S. Public Health Service Publication, March, 1967.[4]

See last page of advertisement for prescribing information.

Ayerst®

The determination of serum lipids

Recently, considerable interest has been shown in the classification of primary hyperlipidemia into five types by Fredrickson and associates.[5] The following chart shows that in three of the four most commonly seen types, triglycerides as well as cholesterol may be elevated. Therefore, triglycerides are also important in making the diagnosis of primary hyperlipidemia.
In studies on 1,000 age-controlled patients, Fredrickson found that hyperlipidemia will be detected in 96 per cent of cases if both serum cholesterol and triglyceride determinations are performed.[7]

Classification of primary hyperlipidemia*

Type	Lipoprotein	Triglycerides	Cholesterol	Carbohydrate Sensitive	Fat Sensitive
I (rare)	Chylomicra elevated	Elevated	Normal	No	Yes
II	Beta lipoproteins elevated	Normal	Elevated	No	Yes
III	Abnormal Beta lipoproteins present	Elevated	Elevated	Yes	Yes
IV	pre-Beta lipoproteins elevated	Elevated	Normal or Elevated	Yes	No
V	Chylomicra and pre-Beta lipoproteins elevated	Elevated	Elevated	Yes	Yes

*Adapted from Fredrickson's 5 Major Categories of Primary Hyperlipidemia.[6]

Atromid-S® (clofibrate)

For the significant reduction of elevated levels of cholesterol and/or triglycerides

Adequately repeated base line studies should be performed to determine if the patient has a significantly elevated serum lipid level. When cholesterol and/or triglyceride levels are found to be elevated, an attempt should first be made to control them with an appropriate dietary regimen.[6] When response is inadequate, lipid-lowering therapy should be initiated with ATROMID-S.
With ATROMID-S therapy:
• you can expect elevated serum cholesterol and/or triglyceride levels to be lowered in responsive patients during the first month of treatment. • you can also expect that the higher the initial level, the greater the fall In xanthomatosis, a reduction in size and/or number of lesions is an indication of response to therapy, and the drug should be administered for an extended period of time, even up to one year.

AN IMPORTANT NOTE: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

The most widely prescribed lipid-lowering agent with seven years of clinical experience

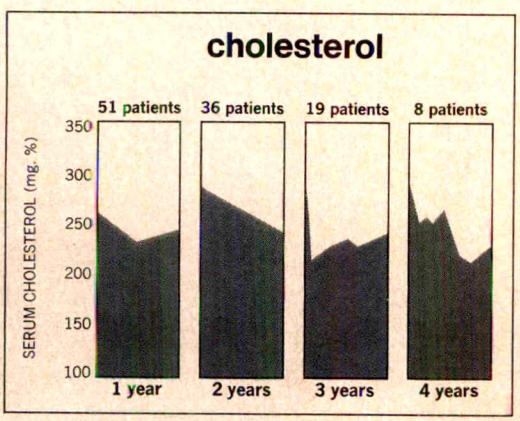
Sustained long term reduction of elevated serum lipid levels with Atromid-S (clofibrate)

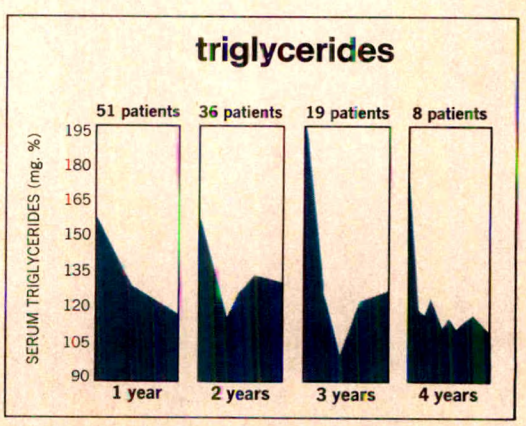
In responsive patients who received ATROMID-S continuously, and who were studied for periods ranging from six months to four years, the lipid-lowering effect was sustained throughout therapy.[8-15]

It has been shown, that lipids return to pretreatment levels when ATROMID-S is discontinued.[8,9,14] According to Oliver,[14] "this clearly indicates the need for continued treatment."

Long term effectiveness*

Of a total of 133 patients treated, there were 114 responders and 19 nonresponders. There were 51 responders in the one year therapy group; 36 responders in the two year group; 19 responders in the three year group; and 8 responders in the four year group.
*Adapted from Oliver.[9]



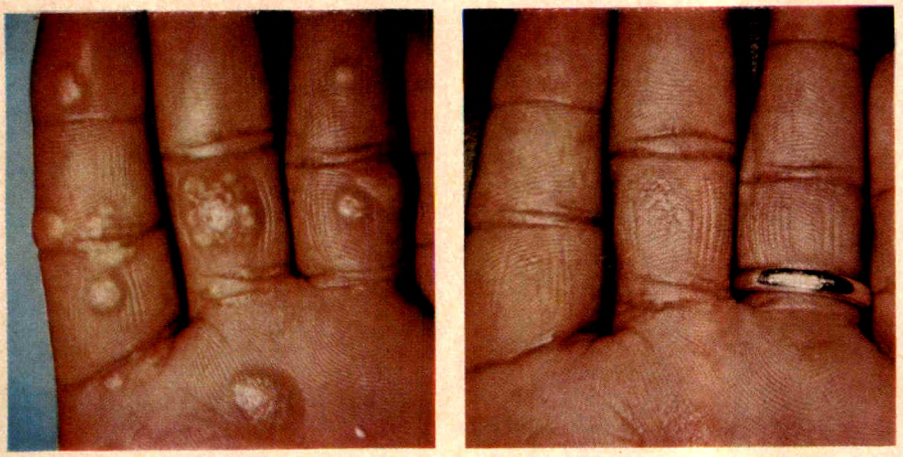


Visible evidence of effectiveness

Oliver[16] is among several investigators who have reported the regression of xanthomata in patients treated with ATROMID-S (clofibrate). This demonstration of regression of xanthomata with ATROMID-S provides visible evidence of the effectiveness of this agent. In some patients, xanthomatous lesions completely disappeared;[9,11,17-19] and in others their size and/or numbers have been reduced.[9-11,19-21]

Regression of xanthomata demonstrated

Before therapy **After therapy**



Male, 39 years old, with long-standing xanthomatous lesions involving elbows, knees, palms and palmar surfaces of the fingers, and buttocks.

Laboratory Data†

2/25/69 cholesterol: 544 mg.%
triglycerides: 315 mg.%
3/11/69 ATROMID-S therapy instituted
9/26/69 cholesterol: 289 mg.%
triglycerides: 129 mg.%

Lesions on palms have disappeared completely. Lesions on elbows and knees are smaller and softer.

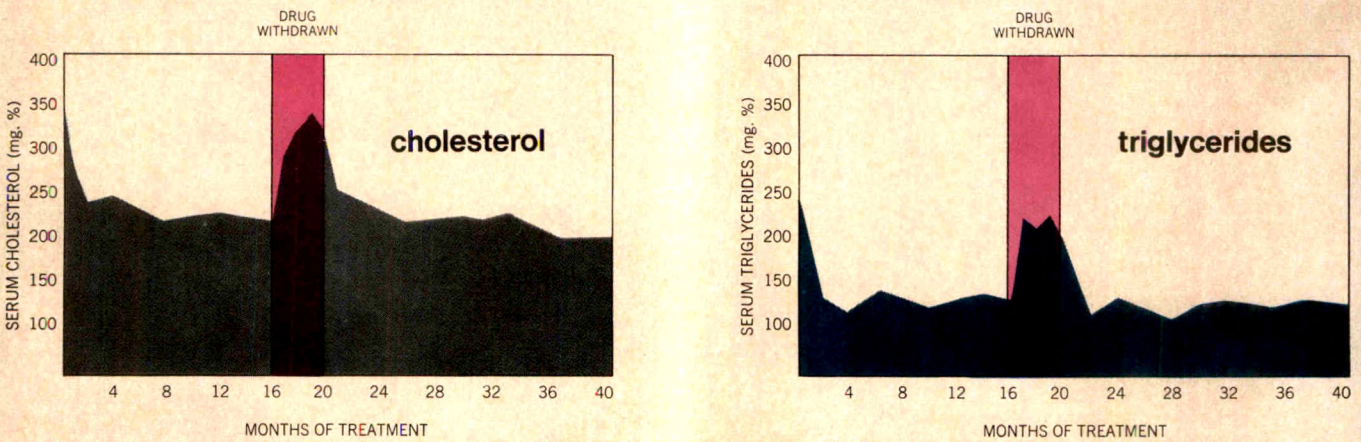
†Case report on file, Medical Department, Ayerst Laboratories, New York, N.Y.

To maintain the lipid-lowering effects—maintain the recommended dosage

One dosage regimen—one capsule Q.I.D.—for all patients at all times. After lipid levels have been reduced, maintain the recommended dosage. A reduction in dosage may result in a rise in lipid levels.

If treatment is interrupted

The interruption of therapy when the patient is under control would permit lipid levels to return to their original pretreatment status. Berkowitz[13] demonstrated the effect of interrupted therapy in the 40 month patient study shown below.



Patient received ATROMID-S (2 Gm. daily) for the first 16 months. Between the 16th and 20th month, therapy was withdrawn completely. From the 20th to the 40th month, ATROMID-S therapy (2 Gm. daily) was resumed.

If given in conjunction with anticoagulants

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

See following page for prescribing information.

Ayerst®

For the reduction of elevated serum cholesterol and/or triglyceride levels

Atromid-S® (clofibrate)

start and maintain therapy with one capsule Q.I.D.

BRIEF DISCUSSION SUMMARY

Indications: ATROMID-S is indicated where reduction of serum lipids is desirable, *e. g.*, patients with hypercholesterolemia and/or hypertriglyceridemia.

Patients with hyperlipemic states involving elevation of both serum triglycerides and serum cholesterol generally have a more favorable response than those with primarily hypercholesterolemia and normal triglyceride levels. However, since response is unpredictable, a therapeutic trial with ATROMID-S should be undertaken in patients with only hypercholesterolemia.

In patients with essential hyperlipemia and xanthomatosis, the skin lesions frequently have regressed on ATROMID-S therapy.

Contraindications: While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

Young women with familial hyperlipemia should not be deprived of this drug, and its use in nonpregnant women in the childbearing age may be undertaken in patients exercising strict birth control procedures. In patients who then plan to become pregnant the drug should be withdrawn several months before conception.

Because pregnancy is a possibility despite birth control precautions, the possible benefits of clofibrate to the patient must be weighed against possible hazards to the fetus in women of childbearing age. Since it is not known if clofibrate is secreted in human milk, the drug should not be given to lactating women.

This drug is not, as yet, indicated for use in children since studies in children have been insufficient.

It is not recommended for use in patients with impaired renal or hepatic function.

Warnings: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE) . THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

Precautions: Before instituting clofibrate therapy, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be made during the first few months of ATROMID-S (clofibrate) administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, treatment should be continued for longer periods (even up to one year) provided there is a reduction in the size of the xanthomata.

During the early stages of ATROMID-S administration, serum transaminase determinations should be made. Mild transient increases in these tests have been noted in some patients. This is thought to be a result of the metabolic effect of the drug rather than a toxic effect. However, if steadily rising or excessive abnormalities occur, the drug should be immediately withdrawn.

Studies in diabetic patients given clofibrate have failed to indicate any effect on insulin or oral hypoglycemic requirements. However, one investigator reported an episode of hypoglycemia occurring two hours after ingestion of 1 Gm. of clofibrate in a patient receiving tolbutamide. Although a causal effect was not established, caution should be observed in diabetic patients.

Adverse Effects: ATROMID-S (clofibrate) has been well tolerated by most patients. The most common side effect is nausea, noted in approximately 5 per cent of cases. Other less common gastrointestinal side effects include vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Headache, dizziness, fatigue, weakness, skin rash, urticaria, pruritus, stomatitis have been reported occasionally. A slight and transient rise in serum glutamic oxaloacetic and/or glutamic pyruvic transaminases has been observed in some patients, but there is no evidence to suggest that this is due to hepatotoxicity. A few instances of increased BSP retention have been reported. One patient receiving butobarbitone, phenobarbital, phenindione, tetracycline, and clofibrate developed agranulocytosis which was attributed by the investigator to the clofibrate. A few cases of leukopenia have been reported, but relationship to ATROMID-S administration has not been established.

Polyphagia and weight gain have been noted in a few patients. It has been suggested that this may be due to increased deposition of subcutaneous fat. However, this has not been established nor has it been definitely determined that the weight gain is drug-related. Instances of weight loss have also been reported. One investigator reported congestive heart failure in a few patients on clofibrate. However, subsequent study by this investigator has shown no increase in circulating plasma volume.

Several instances of muscle cramping, aching, or weakness were reported. One patient with muscle cramps also showed a concomitant rise in SGOT. A few female patients have reported (reversible) dry, brittle hair. Three cases of alopecia areata occurring during ATROMID-S administration have been reported; relationship to this drug has not been established.

Dosage and Administration: *For adult usage only.* The recommended dose is one capsule (500 mg.) four times daily.

Supplied: No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

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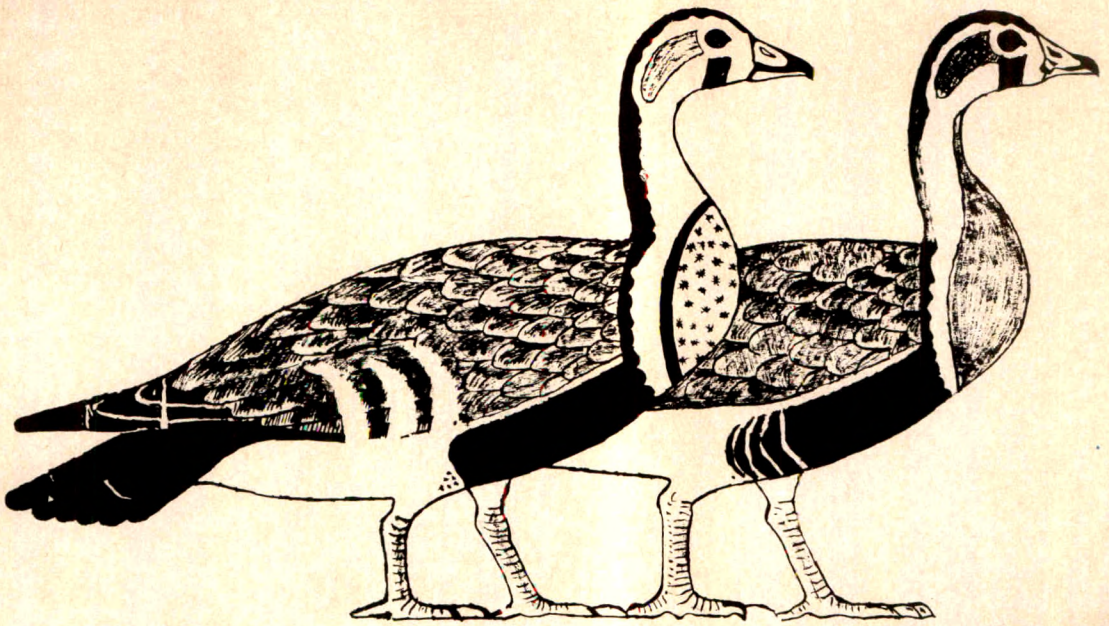
1st of a series

VIDA...*Life for hearts too good to die.*



Ancient man used nature's early warning systems to ward off premature death. In 390 B.C., geese saved the lives of Roman guards at the temple of Juno by alerting them to the stealthy advance of the Gauls.

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Each effervescent tablet in solution supplies 25 mEq. potassium as bicarbonate and citrate

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Each dose in solution supplies 25 mEq. potassium chloride

potassium supplement with chloride

The good-tasting way to treat hypokalemias induced by thiazide diuretics and other drugs...

Here, at last, is a potassium chloride supplement that just doesn't taste like one! The mixed fruit flavor of new K-Lyte/Cl is truly refreshing. Now, K-Lyte/Cl offers your patients all of the therapeutic advantages you expect from a potassium chloride supplement. And you can be sure that your patients will take the K-Lyte/Cl you prescribe—all in good taste.

Now you have a choice...

When extra chloride is not desired, original effervescent K-Lyte is unsurpassed in flavor, effective and safe in short- or long-term potassium supplementation. There is little chance of taste fatigue from K-Lyte with two delicious, effervescent flavors to alternate...fresh-tasting orange and sparkling lime.

K-Lyte® Each effervescent tablet in solution supplies 25 mEq. potassium as bicarbonate and citrate

K-Lyte®/Cl Each dose of powder in solution supplies 25 mEq. potassium chloride

Each tablet or dose must be completely dissolved before taking.

Indications: K-Lyte and K-Lyte/Cl are oral potassium supplements for therapy or prophylaxis of potassium deficiency. Particularly useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses. **Contraindications:** Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause. **Warnings and Precautions:** Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water. K-Lyte/Cl contains 4.9 grams (20 calories) of sucrose per dose which should be considered for patients with restriction of caloric intake. **Adverse Reactions:** Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts. **Dosage and Administration:** Adults: 1 tablet or dose *completely dissolved*, 2 to 4 times daily, depending upon the requirements of the patient: K-Lyte: 1 tablet (25 mEq. potassium) in *3 to 4 ounces of cold or ice water;* K-Lyte/Cl: 1 dose (25 mEq. potassium chloride) in *6 ounces of cold or ice water.* The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: *It is suggested that these products be taken with meals and sipped slowly over a 5-10 minute period.* **How Supplied:** K-Lyte: Effervescent tablets—boxes of 30 and 250 (orange or lime flavors). K-Lyte/Cl: Powder, cans of 30 measured doses with scoop (fruit-punch flavor). Ⓡ

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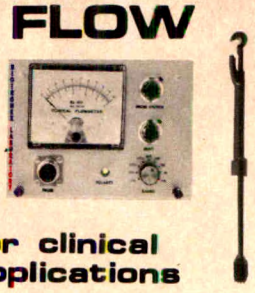

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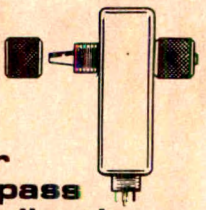

for bypass applications

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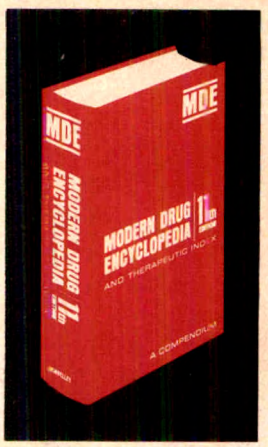

Single-entity drugs in current use are listed alphabetically by generic name in the General Text. Combination drugs are listed by Brand Name. Immediately preceding each drug monograph are listed the Brand-Name Cross-References. Each monograph includes Chemical Name . . . Description . . . Indications . . . Contraindications . . . Precautions . . . Warnings . . . Adverse Reactions . . . Dosage and Administration . . . Brand-Name of Drug . . . Manufacturer.

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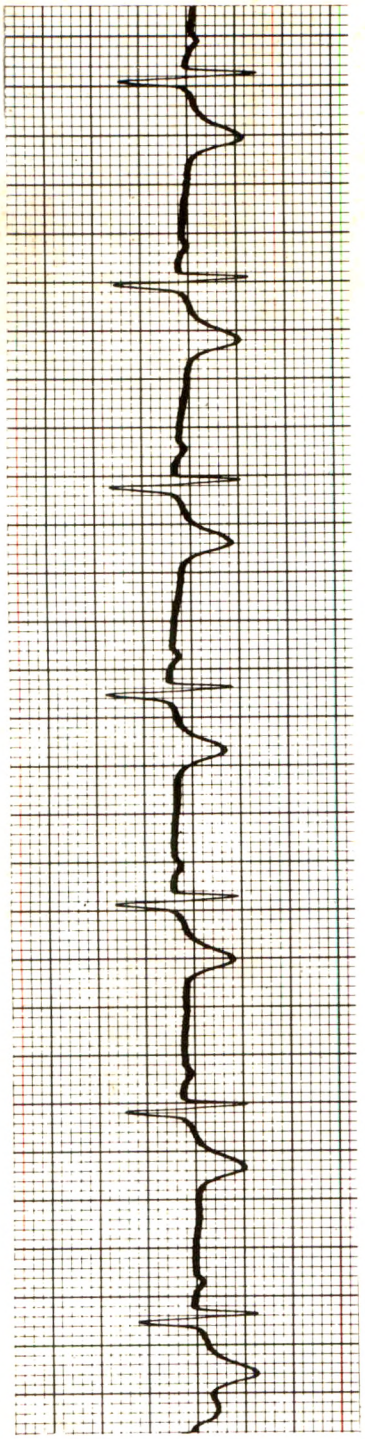

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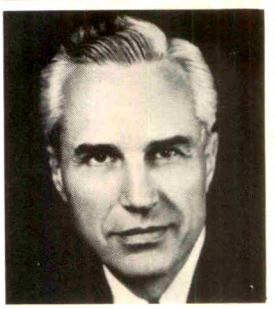

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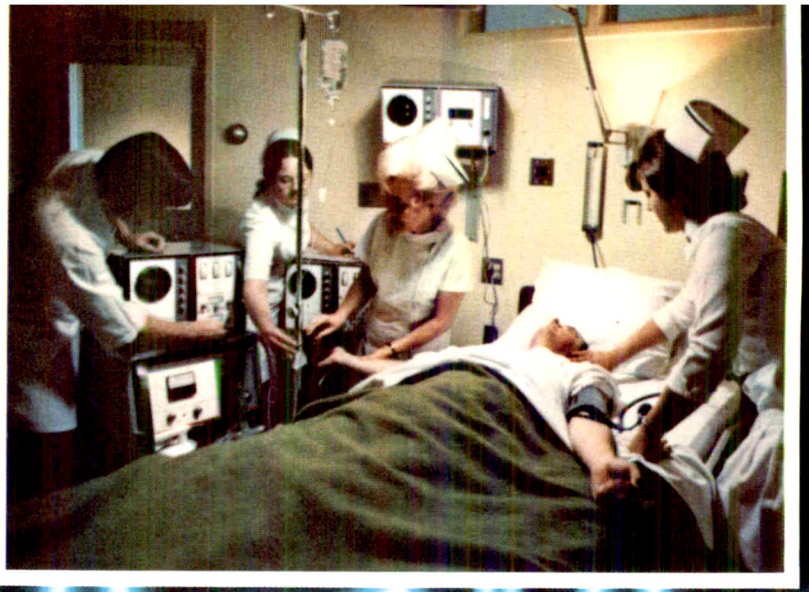

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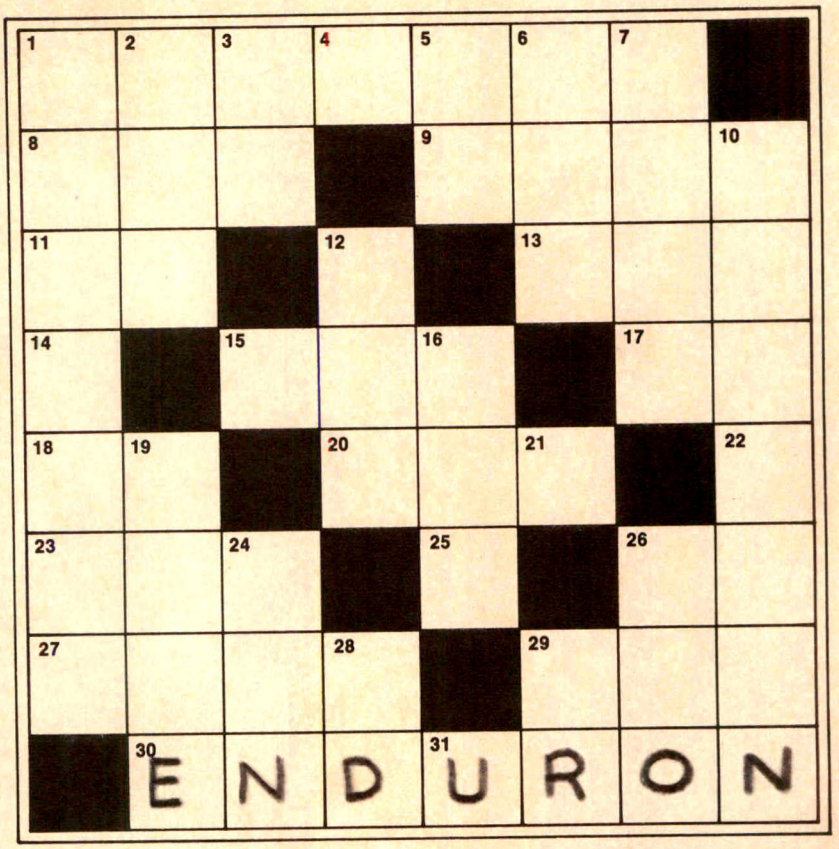

For answer to puzzle, and Brief Summary, see back of this page.

CLUES ACROSS

1. Pertaining to the heart.
8. s.a.: according to _____.
9. Monoamine oxidase inhibitor.
11. Respiratory movement.
12. Bacillus.
13. As needed.
14. A pint.
15. If it is necessary.
17. The _____: lower than subconscious.
18. Test solution.
20. Proof spirit.
22. Dental _ (a single tooth).
23. An atom with positive or negative charge.
25. Rickettsia.
26. Axiolingual.
27. A medicine to be taken in drops.
29. _____ gastric.
30. Abbott thiazide.

CLUES DOWN

1. Principal artery of neck.
2. Golf _____: a form of neuritis.
3. Reading test.
4. O. _____: right eye.
5. Intramuscularly.
6. American Academy of Periodontology.
7. The central mass of necrotic matter in a boil.
10. Protein hormone.
12. _____ sinicus: schistosoma infection in cattle.
15. Without.
16. Alcohol.
19. A lesion of the skin.
21. _____.i.d.: three times a day.
24. _____occlusion: open bite malocclusion.
26. _____sitia: aversion to food.
28. Interpapillary distance.
29. Emil Redlich, Austrian neurologist, 1866-1930.
31. Cat ___.: the amount of digitalis which will kill a cat.

In most cases of mild to moderate hypertension, a diuretic alone will be sufficient.[1]

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1. Schoenberger, J. A.: Management of Essential Hypertension, Med. Clin. of N. Amer., Jan. 1971.

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METHYCLOTHIAZIDE

TABLETS

DESCRIPTION: ENDURON (methyclothiazide) is a member of the benzothiadiazine (thiazide) family of drugs. It is an analogue of hydrochlorothiazide. Clinically, ENDURON is a potent oral diuretic-antihypertensive agent.

ACTION: The predominant effects of ENDURON (methyclothiazide) are diuresis, natriuresis, and chloruresis. The excretion of sodium and chloride is greatly enhanced; potassium excretion is low. Although urinary excretion of bicarbonate is increased slightly, there is usually no significant change in urinary pH. The diuretic and saluretic effects are produced by inhibition of renal tubular reabsorption. There is significant natriuresis and diuresis within two hours after administration of a single dose of methyclothiazide. These effects reach a peak in about six hours and persist for 24 hours following oral administration of a single dose.

In nonedematous patients the "peak" (maximum effective) natriuretic single dose of ENDURON is 10 mg., whereas the "peak" kaliuretic dose is 5 mg. Thus, doubling a single daily dose of 5 mg. results in an increase of sodium output without significantly increasing potassium excretion.

Like other benzothiadiazines, ENDURON also has antihypertensive properties, and may be used for this purpose either alone or to enhance the anti-hypertensive action of other drugs. The mechanism by which the benzothiadiazines, including methyclothiazide, produce a reduction of elevated blood pressure has not been definitely established. Sodium depletion, however, appears to be of primary importance.

ENDURON is readily absorbed from the gastrointestinal tract and is excreted unchanged by the kidneys.

INDICATIONS: ENDURON (methyclothiazide) is indicated in the treatment and control of edema associated with congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, and steroid therapy. The drug also is useful to control edema and hypertension associated with toxemia of pregnancy. It is further indicated as a primary measure in the treatment of mild to moderate hypertension and as an adjunct to other antihypertensive agents in the treatment of severe hypertension. When administered with ENDURON, more potent agents can be given at reduced dosage to minimize undesirable side effects.

CONTRAINDICATIONS: ENDURON (methyclothiazide) is contraindicated in patients with a known sensitivity to methyclothiazide and/or other thiazide diuretics. It should not be used in patients with severe renal disease (except nephrosis) or complete renal shutdown. Thiazide diuretics should not be used in the presence of severe liver disease and/or impending hepatic coma. Hepatic coma has been reported as a consequence of hypokalemia in patients receiving thiazide diuretics.

WARNINGS: The possibility of sensitivity reactions should be considered in patients with a history of allergy or bronchial asthma.

There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts although lesions also occurred spontaneously. Therefore, coated potassium-containing formulations should be administered only when adequate dietary supplementation is not practical, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs.

ENDURON does not contain added potassium.

USE IN PREGNANCY: Enduron should be used with caution in pregnant women and nursing mothers since thiazides cross the placental barrier and appear in cord blood and in breast milk. The use of thiazides may result in fetal or neonatal jaundice, bone marrow depression and thrombocytopenia, altered carbohydrate metabolism in newborn infants of mothers showing decreased glucose tolerance, and possible other adverse reactions which have occurred in the adult. When the drug is used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus.

PRECAUTIONS: Thiazide therapy should be used with caution in patients with severely impaired renal function because of the possibility of cumulative effects. Caution is also necessary in patients with impaired hepatic function or progressive liver disease.

It has been observed that thiazide drugs may reduce arterial responsiveness to levarterenol (nor-epinephrine). Accordingly, the dosage of vasopressor agents may need to be modified in surgical patients who have been receiving thiazide therapy.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the sympathectomized patient.

All patients should be observed for clinical signs of fluid or electrolyte imbalance, including hyponatremia ("low-salt" syndrome). These include thirst, dryness of the mouth, lethargy, and drowsiness.

Hypokalemia may occur during therapy with methyclothiazide. In such cases supplemental potassium may be indicated. Potassium depletion can be hazardous in patients taking digitalis. Myocardial sensitivity to digitalis is increased in the presence of reduced serum potassium and signs of digitalis intoxication may be produced by formerly tolerated doses of digitalis. Hypochloremic alkalosis may occur following intensive or prolonged thiazide therapy. Replacement of chloride may be indicated in such cases.

Thiazides may decrease serum P.B.I. levels without signs of thyroid disturbance.

ADVERSE REACTIONS: Side effects that may accompany thiazide therapy include anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash and photosensitivity. Jaundice and pancreatitis also have been reported.

Blood dyscrasias, including thrombocytopenia with purpura, agranulocytosis, and aplastic anemia, have been reported with thiazide drugs.

Thiazides have been reported, on rare occasions, to have elevated serum calcium to hypercalcemic levels. Serum calcium levels have returned to normal when the medications have been stopped. This phenomenon may be related to the ability of the thiazide diuretics to lower the amount of calcium excreted in the urine.

Elevations of blood urea nitrogen, serum uric acid, and blood sugar have occurred with the use of thiazide drugs. Symptomatic gout may be induced.

Although not established as an adverse effect of methyclothiazide, it has been reported that thiazide diuretics may produce a cutaneous vasculitis in elderly patients.

When adverse reactions occur, they are usually reversible and disappear when the drug is discontinued.

DOSAGE AND ADMINISTRATION: ENDURON (methyclothiazide) is administered orally. The usual adult dose ranges from 2.5 to 10 mg. once daily.

To maintain an edema-free state or as an adjunct in the management of hypertension, 2.5 to 5.0 mg. once daily is often adequate.

Maximum effective single dose is 10 mg.; larger single doses do not accomplish greater diuresis, and are not recommended.

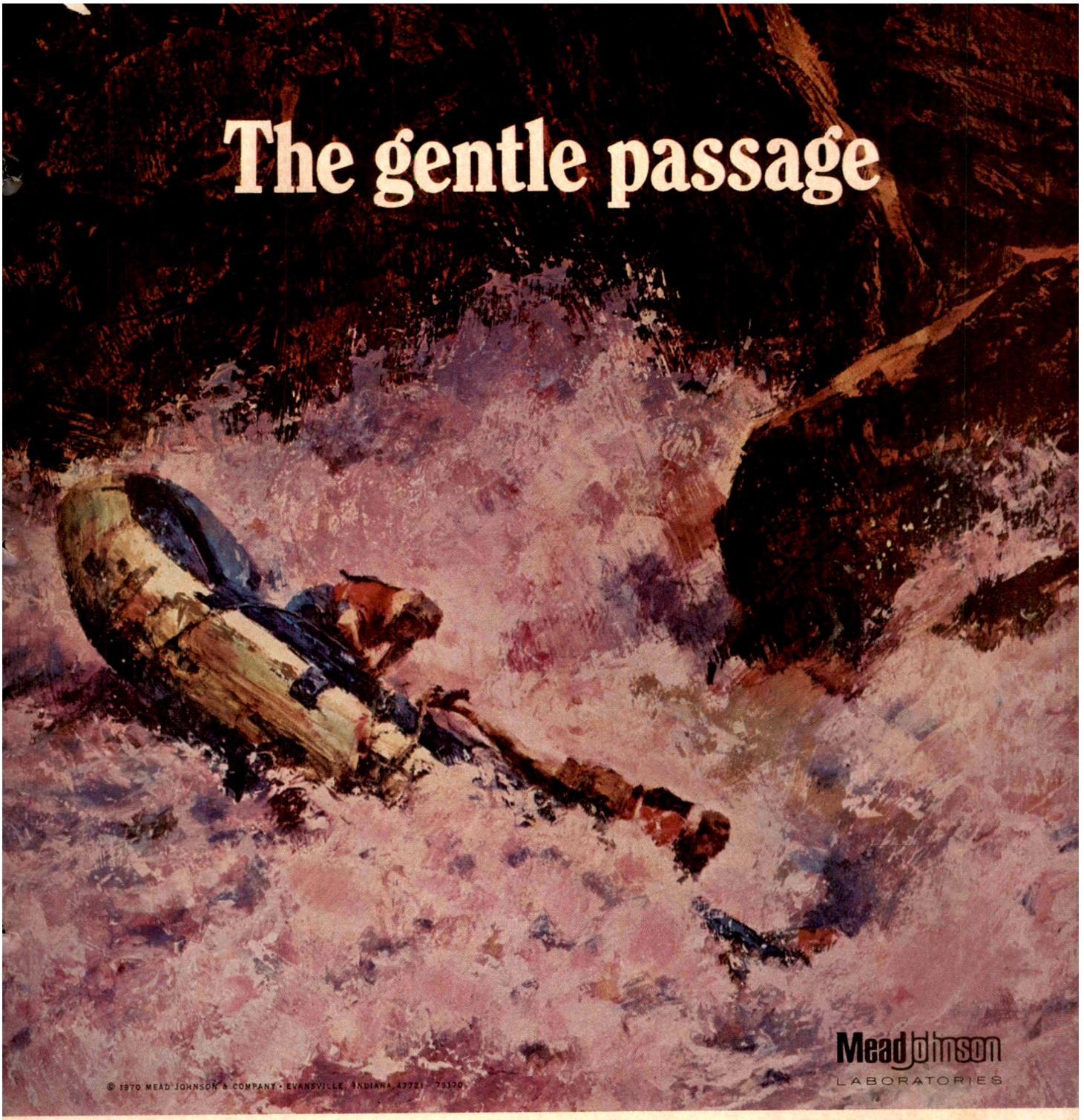
If edema is resistant to methyclothiazide alone, the concomitant administration of an aldosterone inhibitor or glucocorticoid may be of value.

In severely edematous patients or in those with edema resistant to other medication, 10 mg. may be administered twice daily. If this dosage is continued beyond three consecutive days, particular attention should be given to the patient's electrolyte status. Supplemental potassium may be required.

In the treatment of hypertension methyclothiazide may be either employed alone or concurrently with other antihypertensive drugs. Combined therapy may provide adequate control of hypertension with lower dosage of the component drugs and fewer or less severe side effects. An enhanced response frequently follows its concurrent administration with Harmonyl® (deserpidine) so that dosage of both drugs may be reduced.

For treatment of moderately severe or severe hypertension, supplemental use of other more potent antihypertensive agents such as Eutonyl® (pargyline hydrochloride) may be indicated. Such a combination is particularly useful when edema from congestive heart failure or other conditions requiring diuretic therapy coexist with hypertension.

When other antihypertensive agents are to be added to the regimen, this should be accomplished gradually. Ganglionic blocking agents should be given at only half the usual dose since their effect is potentiated by pretreatment with ENDURON 201354



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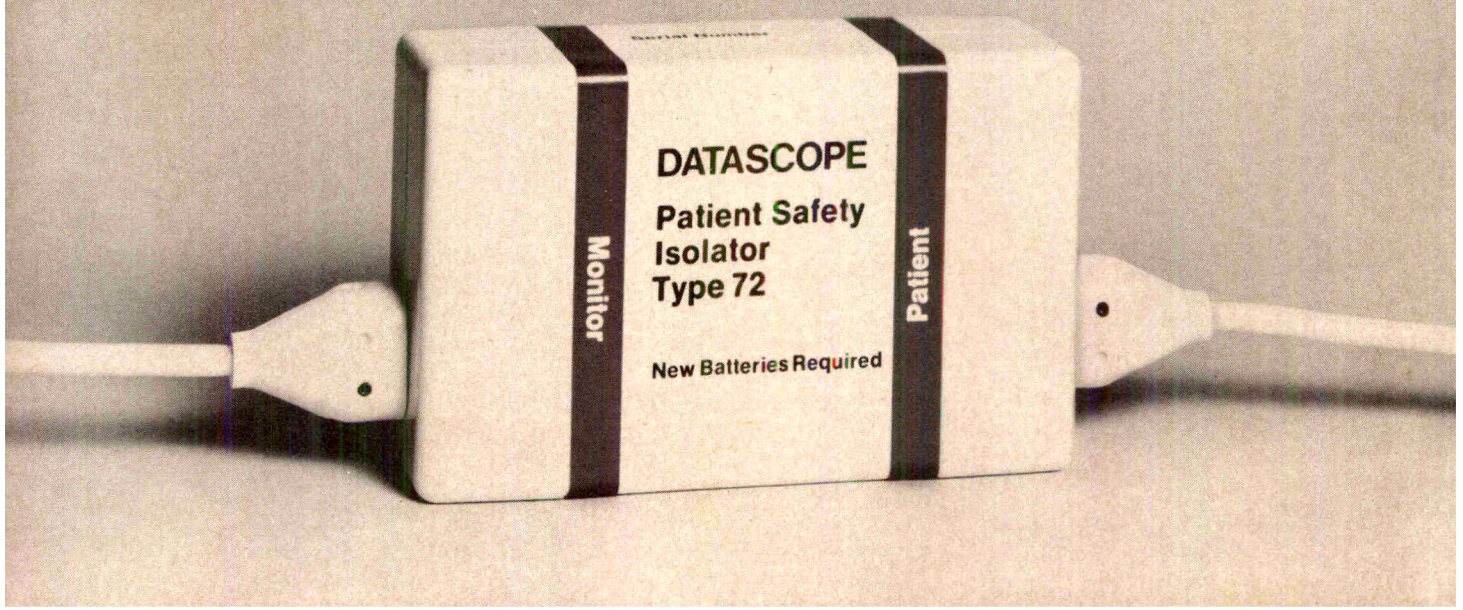

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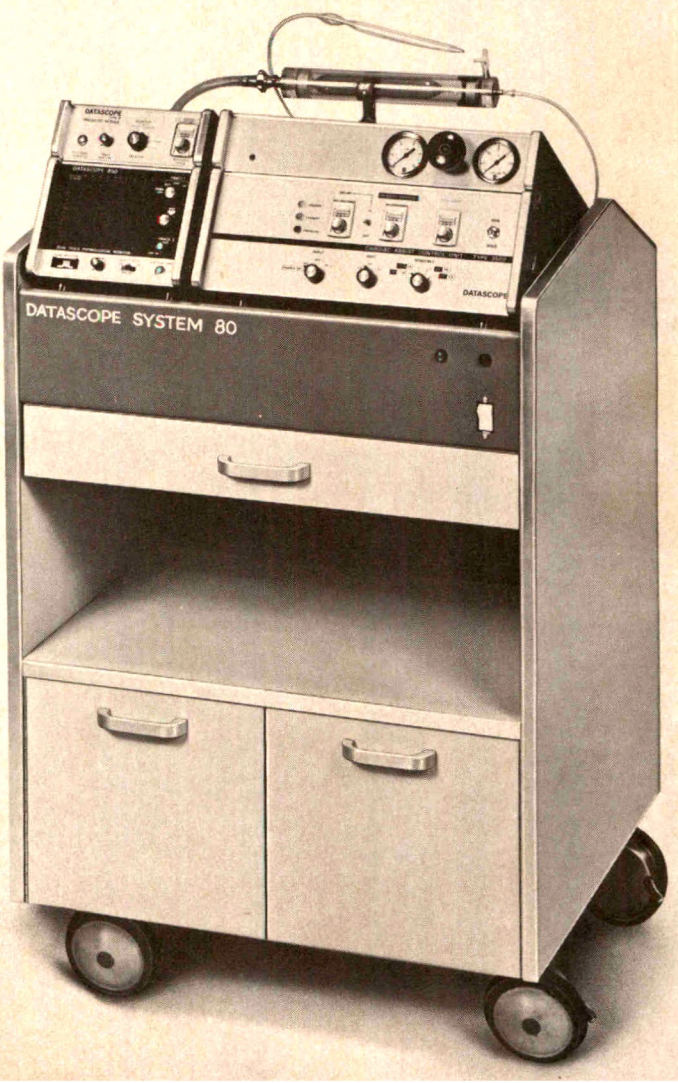
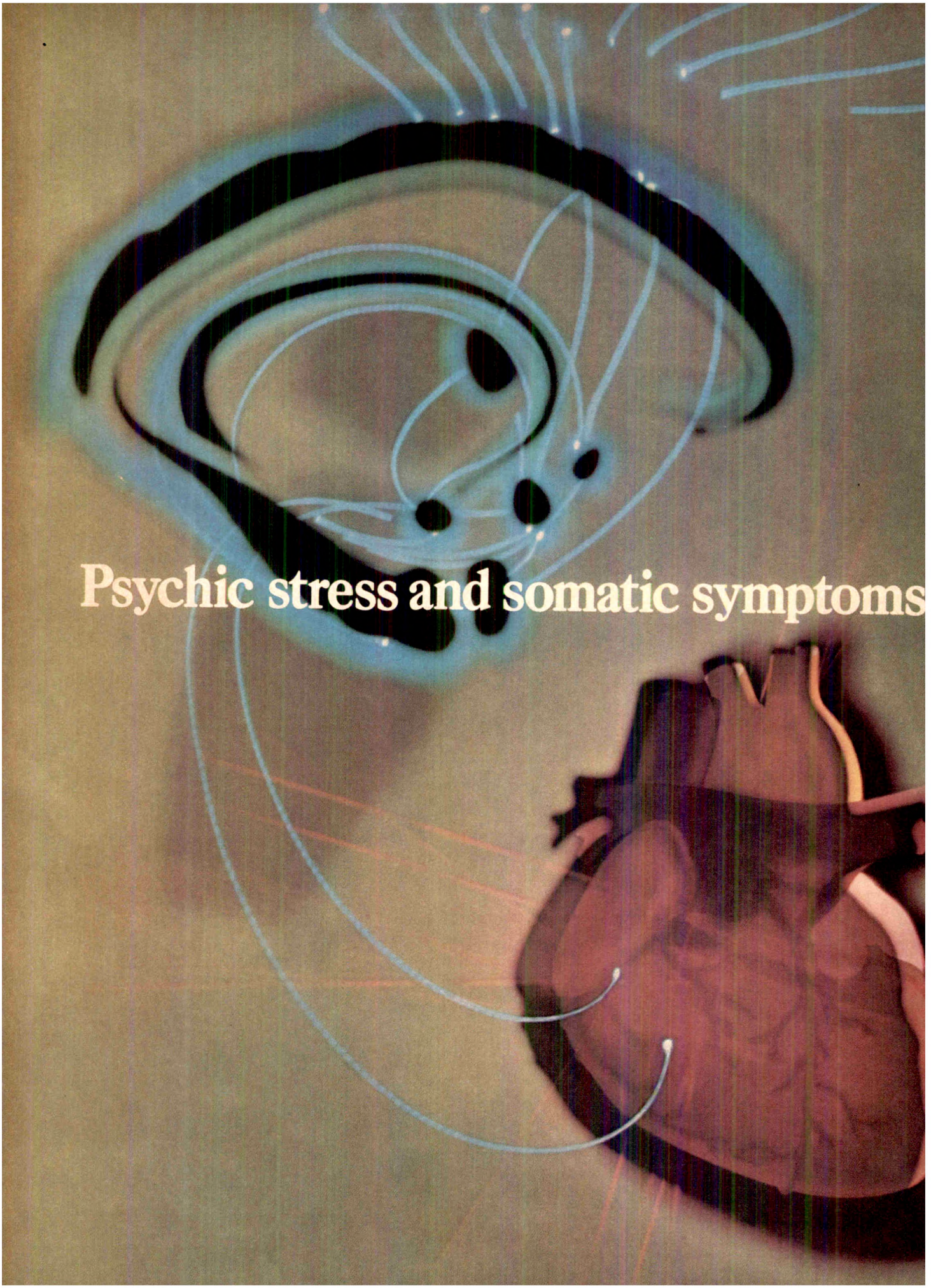
*patent pending

1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

**U.S. Patent #3,347,452

Datascope System 80

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Valium goes to work quickly. Significant improvement is often seen in the first few days of therapy, though some patients may need more time for a clear-cut response.

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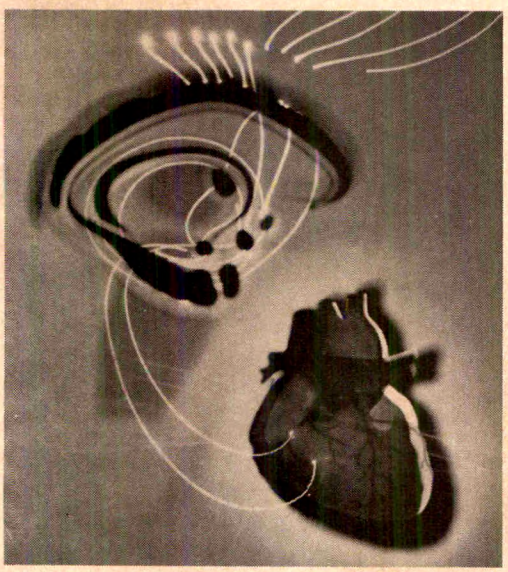
Valium helps relieve tension-produced symptoms—psychic and somatic—in patients overreacting to situational stresses or with psychoneuroses.

Low toxicity

Even at high doses, Valium's lack of toxicity is generally evident. Isolated reports of neutropenia and jaundice make blood counts and liver function tests advisable during long-term therapy. In geriatric patients, usual daily dose is 2 mg to 2½ mg, 1 or 2 times daily initially; increase gradually as needed and tolerated.

Flexible dosage

Available in three convenient tablet strengths—2 mg, 5 mg and 10 mg—Valium permits you to tailor your prescriptions for maximum efficiency.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation, or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states; 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose™ packages of 1000.

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Side effects reported have been mild, transient, and have often proved to be statistically insignificant when compared to placebo effects. (See brief summary on last page of advertisement.)

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a non-barbiturate

Quāālude®-300
(methaqualone) 300 mg. tablets

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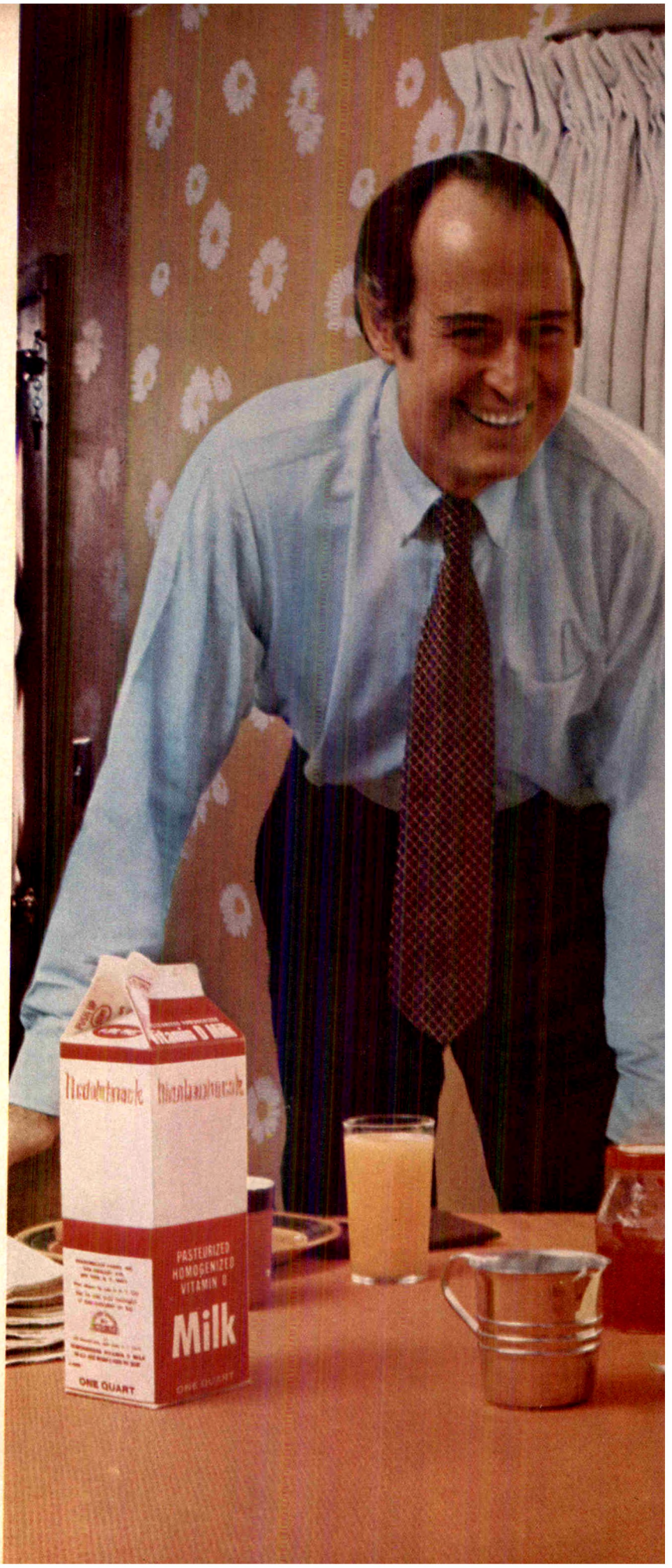
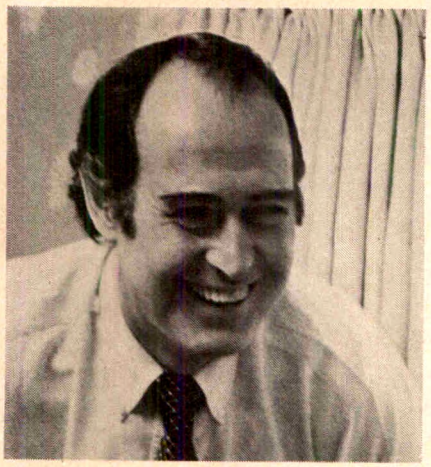
For additional prescribing information, please turn page.



A good morning after a sleep-through night



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Quāālude®-300
300 mg. tablets
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Brief Summary
of Prescribing Information

Indications:
Sleep. Daytime sedation.

Usual Adult Dose:
For sleep, 150-300 mg. at bedtime. For patients previously on other hypnotics, 300 mg. for five to seven nights. *For sedation,* 75 mg. t.i.d. or q.i.d. Not recommended in children. Dosage should be individualized for aged, debilitated or highly agitated patients.

Overdosage:
Acute overdosage may result in delirium and coma, with restlessness and hypertonia, progressing to convulsions. Evacuate gastric contents, maintain adequate ventilation and support blood pressure, if necessary. Dialysis may be helpful. Analeptics are contraindicated. Succinylcholine accompanied by assisted respiration has been proposed for prolonged convulsions. Overdoses of methaqualone appear to be less often associated with cardiac or respiratory depression than are overdoses of oral barbiturates, but shock and respiratory arrest may occasionally occur.

Contraindications:
Contraindicated in women who are or may become pregnant; or patients with known hypersensitivity.

Warnings:
Take hypnotic dose only at bedtime. Not recommended in children. Warn patient on Quāālude against driving a car or operating dangerous machinery. Care needed when administered with other sedative, analgesic or psychotropic drugs or alcohol because of possible additive effects. Pending longer clinical experience, Quāālude should not be used continuously for periods exceeding three months. *Psychological dependence* occasionally occurs. *Physical dependence* rarely reported. However, caution needed with addiction-prone patients.

Precautions:
Use with caution and prescribe small quantities in patients with anxiety states where impending depression or suicidal tendencies exist. Give in reduced doses, if at all, in patients with impaired hepatic function.

Adverse Reactions:
Neuropsychiatric: headache, hangover, fatigue, dizziness, torpor, transient paresthesia of the extremities. An occasional patient has experienced restlessness or anxiety. *Hematologic:* aplastic anemia possibly related to methaqualone has been very rarely reported. *Gastrointestinal:* dry mouth, anorexia, nausea, emesis, epigastric discomfort, diarrhea. *Dermatologic:* diaphoresis, bromhidrosis, exanthema. Urticaria has been particularly well documented.

Supplied:
Quāālude-150 (150 mg. white, scored tablets). Quāālude-300 (300 mg. white, scored tablets).

Consult complete literature before prescribing.

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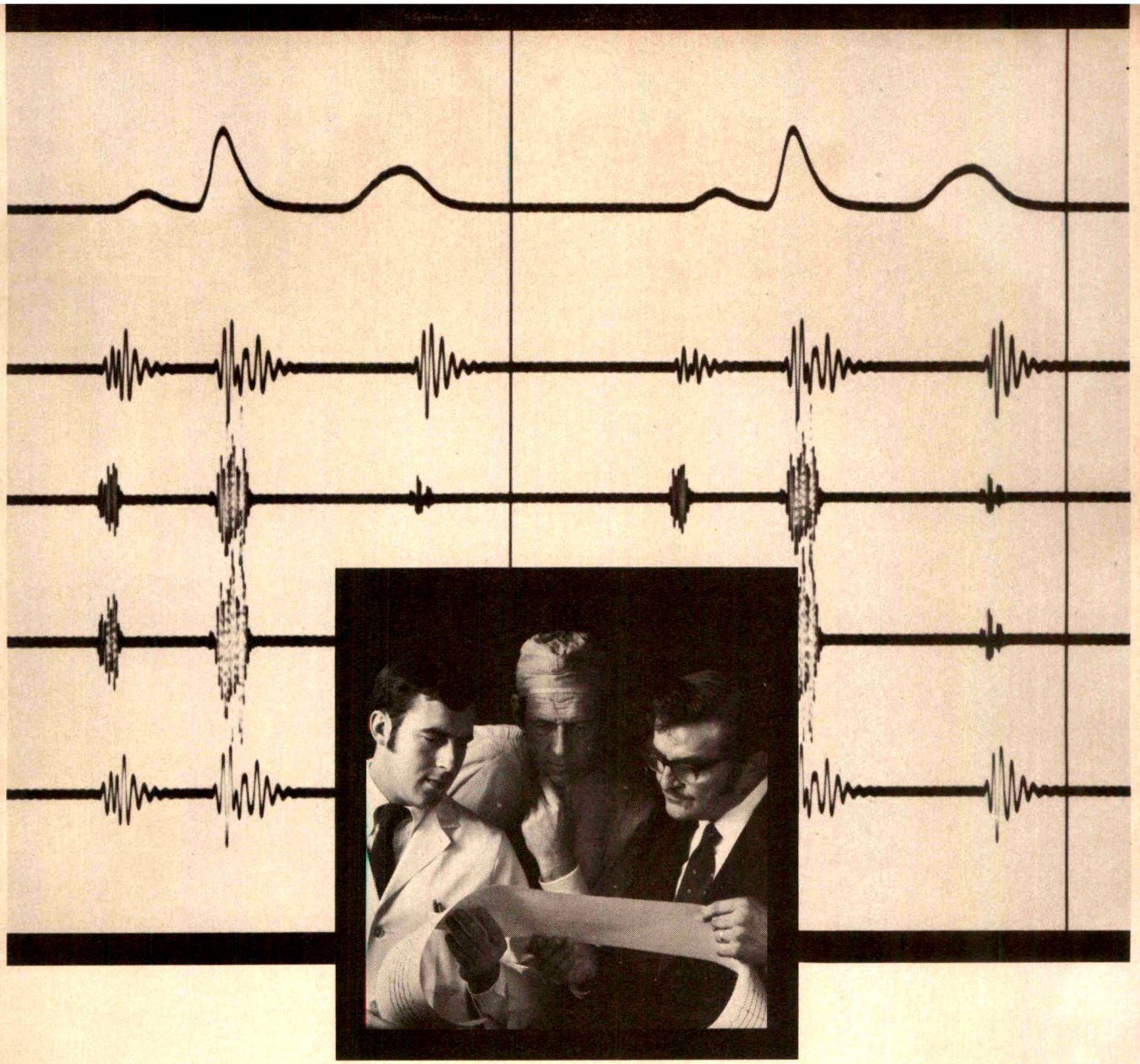

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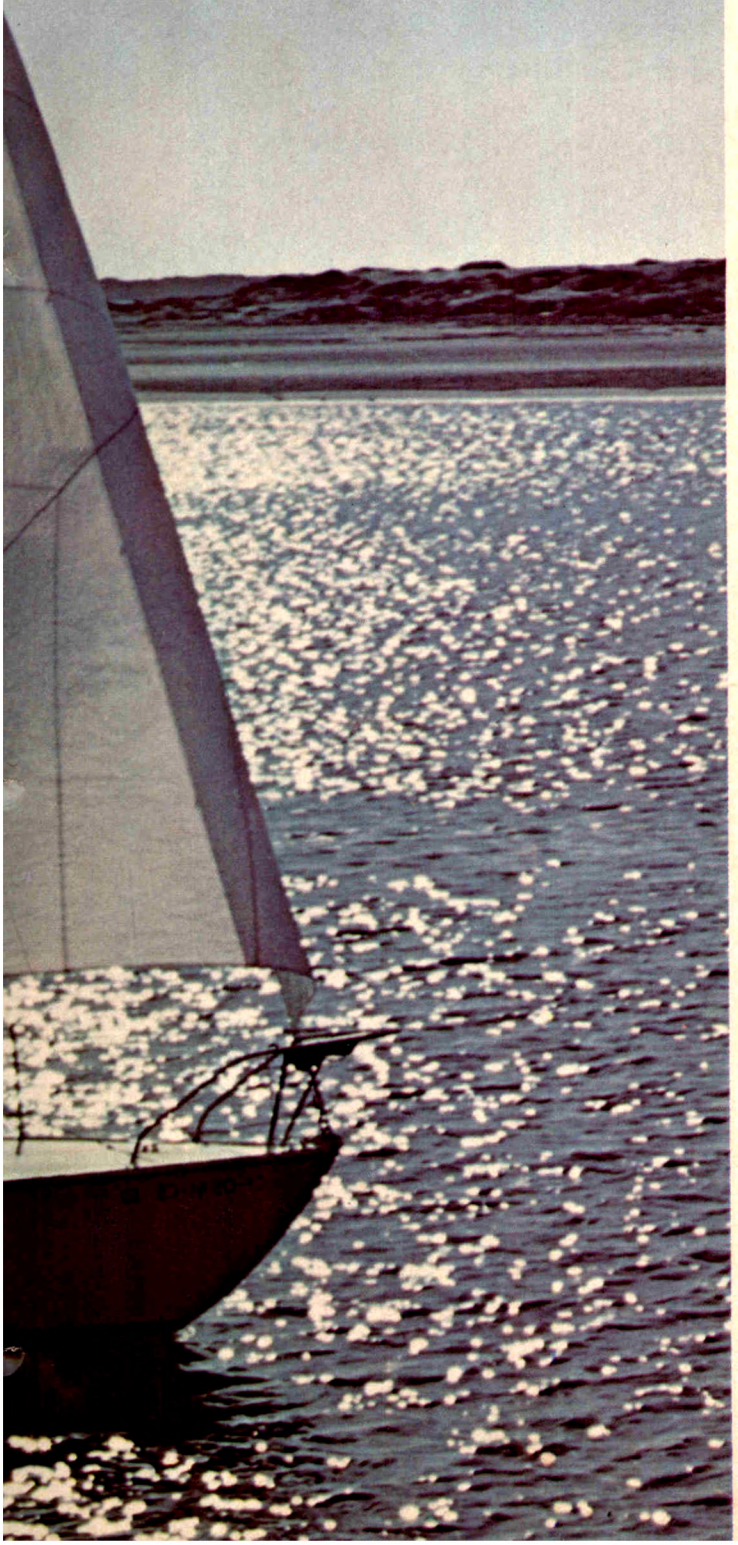

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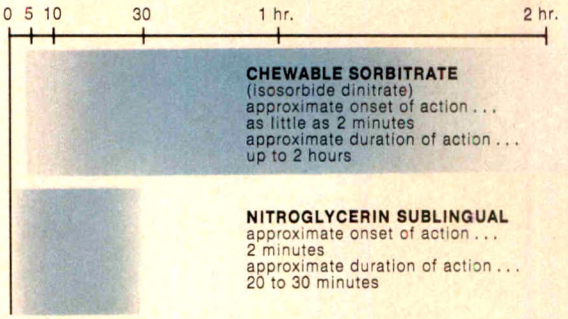

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And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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2 New filmstrip: Cardiopulmonary Resuscitation (CPR)

3 New filmstrip: Arrhythmias Originating in the S-A Node

4 New filmstrip: Arrhythmias Originating in the Atria

5 New filmstrip: Arrhythmias Originating in the A-V Junction

6 New filmstrip: Arrhythmias Originating in the Ventricles

7 New Program Coordinator's Manual and Planning Guide

8 New Learner's Workbook and Planning Guide

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MARCH 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 3

Clinical Studies

Circulatory Effects of Practolol

ROBERT E. FINEGAN, MD
ANTHONY M. MARLON, MD
DONALD C. HARRISON, MD, FACC

Stanford, California

This study was designed to assess the hemodynamic effects of practolol, a beta adrenergic blocking agent that has been shown to be relatively cardioselective and to have more negative chronotropic than negative inotropic effects. Twenty-one patients with heart disease were studied at rest, during exercise and after isoproterenol. Practolol was administered at levels of 200, 400 and 600 μg/kg. The drug had no effect on resting intracardiac pressures, including left ventricular end-diastolic pressure, and it did not affect pulmonary or systemic vascular resistance, stroke work or arteriovenous oxygen difference. Doses of 400 and 600 μg/kg decreased resting heart rate and modified the tachycardia of exercise and isoproterenol. Cardiac index at rest was reduced 13 percent by higher doses. The first derivative of left ventricular pressure development (dp/dt) fell slightly, but only during exercise. In 2 patients, the competitive interaction between isoproterenol and practolol was shown by stepwise administration of increments of each drug. These data demonstrate that practolol, in appropriate doses, can be used in patients with heart disease to produce competitive beta blockade without concomitant deterioration of ventricular function.

The clinical use of beta adrenergic blocking agents has provided new approaches to the treatment of several important cardiovascular disorders including arrhythmias, angina pectoris, hypertrophic obstructive cardiomyopathies and hypertension.[1-3] Although a number of drugs with beta adrenergic blocking action have been studied, propranolol has been used most widely in clinical practice. Recently, other agents have been synthesized, and their cardiovascular action has been studied in the search for a drug with selective beta adrenergic blocking properties. Propranolol blocks the excitatory beta adrenergic receptors of the heart, resulting in both negative chronotropic and negative inotropic effects. In addition, it blocks the peripheral beta adrenergic receptors which mediate smooth muscle relaxation in blood vessels and bronchioles.[4]

Practolol, 4-(2-hydroxy-3-isopropyl amino-propoxy) acetanilide, ICI, 50,172, or AY 21,011, is a recently synthesized drug that

From the Cardiology Division, Stanford University School of Medicine, Stanford, Calif. This work was supported in part by National Institutes of Health Grants HE-5709, HE-05866, HE-09058, and Grant 67-708 from the American Heart Association. Manuscript received February 5, 1971, accepted April 7, 1971.

Address for reprints: Donald C. Harrison, MD, Chief, Cardiology Division, Stanford University School of Medicine, Stanford, Calif. 94305.

TABLE I

Hemodynamic Data in 19 Patients Before and After Practolol: At Rest and During Exercise and in Response to Isoproterenol

Case no.	Diag.	Cardiac Rhythm	Pract	Cond.	Pressures (mm Hg) RA	RV S/ED	PA S/D/M	PAW	LV S/ED	Ao S/D/M	HR	CO	CI	SV	SI	PVR	SVR	$AVO_2\Delta$	SWI	dp/dt
1	MS	Sinus	0	Rest	2	79/9	79/30/50	30	108/7	108/70/88	70	5.8	3.2	66.2	37	4.3	18	3.9	44.3	1135
			0	Iso	...	...	...	...	...	...	120	...	...	...	...	...	...	...	...	1437
				Ex	4	82/7	82/40/57	40	108/6	100/70/90	100	5.3	3.0	54.0	30	3.2	16	...	36.7	1125
			160	Rest	4	54/8	47/22/33	28	90/7	82/52/72	72	6.0	3.4	84.0	47	0.8	11	...	46.0	812
				Iso	...	...	...	...	...	...	90	...	...	...	...	...	...	...	...	843
				Ex	4	72/7	72/35/48	33	98/8	94/58/74	76	6.0	3.4	81.0	45	2.5	11	...	45.3	1223
2	MS	Sinus	0	Rest	3	37/5	37/13/19	13	114/6	118/72/87	66	3.8	2.5	58.0	38	1.6	22	5.7	45.0	1012
				Ex	...	45/6	45/–/–	22	116/10	110/72/96	84	5.6	3.7	67.0	44	...	...	8.5	57.5	1063
			160	Rest	...	...	37/15/22	15	112/5	...	73	3.5	2.3	50.0	32	2.0	...	6.1	...	1025
				Ex	4	38.6	42/18/24	20	121/5	116/74/96	86	4.4	2.9	52.0	34	1.4	21	9.5	44.4	1128
3	MS	AF	0	Rest	6	43/4	42/18/27	19	142/8	142/66/104	72	4.8	2.6	65.0	35	1.7	20	4.9	49.5	1038
				Ex	13	...	69/35/47	28	140/14	154/86/112	102	5.3	2.9	52.0	28	3.6	19	9.5	42.7	1126
			160	Rest	6	38/4	40/18/27	17	136/8	...	72	4.1	2.2	52.0	28	2.4	...	4.1	...	864
				Ex	13	62/10	65/25/38	23	...	144/70/96	76	5.0	2.7	66.0	36	3.0	17	10.0	47.0	...
4	MS	Sinus	0	Rest	5	33/4	33/14/20	12	148/10	144/68/98	78	3.3	2.1	42.4	27	2.4	28	5.9	36.0	948
				Ex	4	39/–	38/24/29	22	174/16	170/84/116	78	3.3	2.1	42.4	27	2.1	34	10.5	42.6	1012
			200	Rest	5	36/8	38/14/26	19	157/8	156/80/112	66	3.2	2.1	50.2	32	2.2	33	6.4	48.7	903
				Ex	5	35/5	35/17/23	18	160/12	160/90/110	90	3.7	2.4	63.1	41	1.4	28	9.6	61.3	1045
5	MS	AF	0	Rest	6	37/6	42/20/27	19	110/8	110/70/85	84	3.1	1.7	36.8	20	3.9	25	6.9	23.1	807
				Ex	10	96/8	96/48/65	..	150/14	150/84/100	150	5.7	3.1	38.6	21	3.0	16	14.5	28.6	1298
			400	Rest	6	37/4	44/23/29	18	112/8	124/78/96	90	3.0	1.6	33.1	18	3.7	30	7.5	23.5	1279
				Ex	11	70/9	73/41/51	...	160/13	156/80/120	132	5.0	2.7	36.8	20	2.0	22	17.1	32.6	1246
6	MS	AF	0	Rest	6	46/5	48/22/31	20	98/8	118/70/86	90	4.8	2.4	53.2	27	1.9	17	6.9	31.6	773
				Ex	12	110/13	110/46/72	...	...	138/94/108	162	5.2	2.6	32.4	16	...	18	17.5	23.5	...
			400	Rest	8	43/9	50/27/34	21	110/13	108/72/86	64	...	...	...	...	...	...	...	...	797
				Ex	16	90/14	100/50/68	...	130/12	128/86/100	132	5.1	2.6	39.4	20	...	16	18.3	27.2	1209
7	MS	AF	0	Rest	8	57/10	54/26/36	21	115/9	132/72/94	78	3.6	1.9	45.1	24	4.2	24	6.1	30.7	944
				Ex	13	68/18	78/43/51	37	135/20	158/94/114	96	...	...	...	..	...	...	9.8	...	1013
			400	Rest	11	55/12	61/39/37	28	...	122/68/90	78	3.0	1.6	39.5	21	3.7	26	7.0	25.7	...
				Ex	18	74/18	80/42/58	32	...	140/74/102	80	3.3	1.7	39.5	21	7.7	25	11.6	29.1	...
8	MS	AF	0	Rest	4	30/4	30/14/24	18	108/7	108/78/100	114	4.0	2.2	34.9	19	1.5	24	5.3	25.8	1183
				Ex	6	48/8	50/29/38	27	136/12	136/90/100	168	7.1	3.9	42.3	23	1.5	13	10.5	31.3	1388
			400	Rest	4	24/3	24/19/19	12	112/12	118/88/98	90	4.1	2.2	44.2	24	1.7	23	5.0	32.0	1032
				Ex	9	53/8	53/30/38	27	124/16	124/88/109	144	6.1	3.2	40.5	22	1.8	16	10.5	31.1	1109

9	MS	AF	0	Rest	4	50/8	50/21/33	27	110/18	106/64/86	68	4.0	2.6	53	34	1.5	21	5.4	39.8	705
				Ex	8	50/9	57/28/41	30	126/22	126/80/96	90	5.6	3.6	62	40	2.0	16	7.0	52.2	1018
			400	Rest	6	...	41/18/30	22	110/8	110/70/86	78	3.9	2.5	50	32	2.0	20	5.9	37.4	846
				Ex	6	42/4	60/32/45	...	120/10	136/80/100	84	4.8	3.1	58	37	...	20	7.9	50.3	1076
10	MS	AF	0	Rest	7	48/9	55/20/36	26	126/8	126/78/100	88	4.7	3.1	54	35	2.1	20	4.5	47.6	1079
			400	Rest	6	30/6	35/15/24	20	116/8	110/64/88	72	3.7	2.5	54	35	1.1	22	5.6	41.9	862
11	MS	Sinus	0	Rest	8	42/11	41/23/36	30	100/12	93/60/73	68	4.1	2.6	59	38	1.5	16	4.1	37.7	814
				Iso	...	...	...	...	96/6	...	104	...	...	...	...	...	...	...	...	975
				Ex	10	62/12	63/34/48	...	101/13	101/69/83	100	4.5	2.9	45	29	...	16	4.5	32.7	1390
			400	Rest	8	40/8	46/23/28	25	88/10	92/54/72	78	3.7	2.4	48	31	0.8	17	3.7	30.4	650
				Iso	...	...	...	...	90/6	...	93	...	...	...	...	...	...	...	...	825
				Ex	13	...	67/39/52	...	95/12	104/66/84	110	5.1	3.3	47	30	...	14	5.1	34.3	925
12	MS	AF	0	Rest	8	47/9	50/27/37	22	122/16	124/90/101	64	3.0	1.8	47	28	5.0	29	6.9	38.5	756
				Iso	...	...	...	...	...	...	96	...	...	...	...	...	...	...	...	...
			400	Rest	9	50/9	51/28/39	24	115/14	115/86/96	60	3.2	1.9	54	32	4.7	24	7.8	41.8	850
				Iso	...	...	...	...	...	...	93	...	...	...	...	...	...	...	...	...
13	MS	AF	0	Rest	6	39/5	38/15/29	21	122/9	...	80	3.6	2.1	44	26	2.2	...	4.7	...	975
				Iso	...	...	...	...	98/6	...	150	...	...	...	...	...	...	...	...	1225
			600	Rest	6	36/6	35/19/26	20	132/10	132/78/96	66	3.5	2.1	54	32	1.7	...	5.5	41.8	875
				Iso	...	...	...	...	...	106/60/–	84	...	...	...	...	...	...	...	...	...
14	AS	Sinus	0	Rest	6	42/9	42/19/26	20	180/18	92/52/70	60	5.2	2.9	85	48	1.2	12	4.3	45.7	...
				Iso	...	...	42/24/30	...	...	77/42/61	80	...	...	...	...	...	...	...	...	...
			600	Rest	4	43/5	44/18/21	18	...	99/56/78	60	5.0	2.8	84	47	0.6	15	4.6	49.9	...
				Iso	...	...	36/18/–	...	...	81/48/66	80	...	...	...	...	...	...	...	...	...
15	CAD	Sinus	0	Rest	2	15/4	14/4/6	2	101/7	112/70/80	90	8.0	4.1	92	47	0.5	9.0	3.4	51.1	...
				Iso	...	...	...	...	...	...	94	...	...	...	...	...	...	...	...	...
				Ex	3	27/5	24/10/15	8	135/19	132/72/105	108	11.6	6.0	107	55	0.6	8.6	7.8	78.5	...
			600	Rest	0	15/2	12/4/6	2	100/6	100/60/81	77	7.1	3.6	92	47	0.6	11.5	3.5	51.8	...
				Iso	...	...	...	...	...	...	84	...	...	...	...	...	...	...	...	...
				Ex	4.5	24/4	20/9/14	8	118/13	107/56/80	94	10.2	5.3	109	56	0.6	7.5	7.1	60.9	...
16	MR	AF	0	Rest	4	27/5	29/12/18	12	100/6	102/70/80	84	4.6	2.4	55.4	29	1.3	16	6.5	31.6	...
				Iso	...	...	...	...	...	...	96	...	...	...	...	...	...	...	...	...
				Ex	3	...	49/18/27	...	111/12	109/74/88	90	6.6	3.5	74.5	39	...	13	11.2	46.7	...
			600	Rest	...	...	28/12/17	10	96/7	96/58/76	60	2.9	1.5	47.7	25	2.9	25	7.7	25.8	...
				Iso	...	...	...	...	...	...	78	...	...	...	...	...	...	...	...	...
				Ex	12	...	45/18/28	...	110/16	110/68/80	72	5.2	2.7	72.6	38	...	13	13.0	41.2	...
17	MR	AF	0	Rest	3	32/4	32/8/17	14	128/14	128/72/84	120*	3.8	2.5	33.0	21	0.8	...	5.5	24.0	1180
				Iso	...	...	.../.../13	...	114/10	...	140*	...	...	...	...	...	...	...	...	1025
				Ex	5	37/6	32/14/22	19	152/10	...	144*	5.6	3.6	...	25	0.5	...	10.0	...	1650
			400	Rest	3	17/3	18/11/13	10	116/6	...	90*	3.2	2.0	...	22	0.9	...	6.2	...	1050
				Iso	...	...	.../.../14	...	120/6	...	114*	...	...	...	...	...	...	...	...	1185
				Ex	4	24/6	...	20	128/10	...	92†	4.2	2.6	...	28	...	...	8.9	...	1111

continued

Case no.	Diag.	Cardiac Rhythm	Pract	Cond.	Pressures (mm Hg) RA	RV S/ED	PA S/D/M	PA PAW	LV S/ED	Ao S/D/M	HR	CO	CI	SV	SI	PVR	SVR	$AVO_2\Delta$	SWI	dp/dt
18	IHSS	Sinus	0	Rest	6	40/6	28/17/22	12	134/22	130/80/105	94	5.0	3.2	52	33	2.0	20	4.4	47.1	1135
				Iso	...	...	...	...	144/22	...	120	...	...	...	...	...	...	...	...	1565
				Ex	8	52/10	54/27/34	...	172/40	172/110/130	110	5.8	3.7	53	34	...	21	9.9	60.1	1407
			400	Rest	9	27/9	27/19/22	13	118/16	118/84/100	76	3.8	2.4	49.9	32	2.4	24	5.5	43.5	1111
				Iso	...	...	...	...	124/28	...	96	...	...	...	...	...	...	...	...	938
				Ex	10	47/11	50/20/36	25	140/41	140/94/117	104	4.9	3.1	46.8	30	2.2	22	11.7	47.7	1185
19	AI	Sinus	0	Rest	4	23/7	23/9/13	11	147/20	147/53/86	60	5.4	2.6	87.3	43	0.4	15	5.3	50.3	1450
				Iso	...	...	...	...	...	132/45/–	84	...	...	...	...	...	...	...	...	...
				Ex	7	32/–	32/12/18	12	190/16	157/60/102	96	7.9	3.9	83.2	41	0.8	12	8.3	56.9	1822
			400	Rest	4	24/7	20/9/14	11	162/30	146/54/90	66	4.9	2.4	73.1	36	0.6	19	5.7	44.1	1037
				Iso	...	...	...	...	...	126/48/85	84	...	...	...	...	...	...	...	...	...
				Ex	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

* = atrial fibrillation; † = normal sinus rhythm.

AF = atrial fibrillation; AI = aortic insufficiency; Ao = arterial pressure; AS = valvular aortic stenosis; $A\text{-}VO_2\Delta$ = arteriovenous oxygen difference in volume percent; CAD = coronary artery disease; CI = cardiac index (liters/min per m^2); CO = cardiac output (liters/min); Cond = experimental condition; dp/dt = maximal rate of pressure rise in left ventricle (mm Hg/sec); Diag. = diagnosis; D = diastolic; ED = end-diastolic; Ex = exercise; HR = heart rate (beats/min); IHSS = idiopathic hypertrophic subaortic stenosis; Iso = isoproterenol; LV = left ventricle; M = mean; MR = mitral regurgitation; MS = mitral stenosis; Pa = pulmonary arterial; PAW = mean pulmonary arterial wedge; Pract = dose of practolol (μg/kg); PVR = pulmonary vascular resistance (arbitrary units); RA = mean right atrial; RV = right ventricle; S = systolic; SI = stroke index, cc/min per m^2; SV = stroke volume (cc per min); SVR = systemic vascular resistance (arbitrary units); SWI = stroke work index (g-m/m^2).

has been found to block predominantly excitatory beta receptors and thus be relatively cardioselective.[5–7] This drug may have advantages in the patient with asthma or chronic obstructive airway disease when beta adrenergic blockade is desired. Furthermore, it has been suggested[8,9] that practolol has more negative chronotropic than inotropic activity when compared to propranolol. It has been given to patients with congestive heart failure and after a myocardial infarct[10,11] without significant side effects.

This hemodynamic study was designed to measure the circulatory effects of practolol during rest and supine exercise in patients undergoing cardiac catheterization in order to obtain a clearer understanding of the action of the drug in patients with cardiac disease.

Materials and Methods

Twenty-one patients (11 women and 10 men) were selected for the study group. All the patients were hospitalized for evaluation of heart disease, and their status was considered to be class II or III (New York Heart Association classification). Clinical evaluation included history, physical examination, electrocardiography, phonocardiography and a cardiac X-ray series. Ages ranged from 25 to 66 years (mean 45 years). Fourteen of these patients had mitral stenosis without other valvular lesions or evidence of left ventricular disease, 2 had mitral regurgitation, 1 aortic insufficiency, 1 idiopathic hypertrophic subaortic stenosis, 1 valvular aortic stenosis, 1 hypertension and 1 coronary artery disease. All studies were performed during diagnostic cardiac catheterization.

After the patient had given informed consent to the administration of practolol as part of this evaluation, standard techniques were used for right heart catheterization. Pulmonary wedge pressure determinations were obtained in all patients for assessment of left atrial pressure, and the left ventricle was catheterized by retrograde techniques from the brachial artery. The first derivative of left ventricular pressure development (dp/dt) was determined by computer analysis of the left ventricular pressure curve. Data were obtained at rest and during bicycle exercise before and after administration of practolol* through the right heart catheter over a 10 minute period. Exercise was performed when possible with the patient in a supine position on a calibrated bicycle ergometer for 10 minutes. Hemodynamic measurements were made only after 5 minutes of steady exercise at a level that the physician estimated the patient could perform. Four patients received a low dose (160 to 200 μg/kg), 11 a moderate dose (400 μg/kg) and 6 a large dose (600 μg/kg) of practolol. Hemodynamic measurement was begun 15 to 20 minutes after completion of the drug infusion. An isoproterenol challenge of 3 μg was administered as a single rapid injection through the right heart catheter to assess the degree of beta adrenergic blockade before and after the administration of practolol. Cardiac output was measured by the Fick method, except for 2 patients who received graded doses of isoproterenol to

* Kindly supplied as AY21, 011 by Dr. R. O. Davies of Ayerst Laboratories, Montreal, Canada.

evaluate the competitive nature of the beta blockade produced by practolol. In these patients, cardiogreen dye was used to measure cardiac output. These patients received practolol in 2 increments of 300 μg/kg, so that measurements were made in control conditions and after administration of 300 and 600 μg/kg. Response to graded doses of isoproterenol infusion (0.005 to 0.04 μg/kg per min) for 5 minutes was measured during control periods and after the administration of the 2 levels of practolol, 300 and 600 μg/kg.

Results

Clinical and hemodynamic data are listed for each patient studied in Table I. A summary of the hemodynamic changes and their significance during rest and exercise, both before and after the administration of practolol are shown in Table II. None of these measurements, including intracardiac and arterial pressures, stroke index, stroke work, vascular resistance or arteriovenous oxygen difference were affected by the administration of practolol, either at rest or during exercise. However, the drug did decrease heart rate significantly when given in a dose of 400 to 600 μg/kg during all 3 experimental conditions of rest, exercise and isoproterenol challenge (Fig. 1). Smaller doses (160 to 200 μg/kg) did not affect heart rate in 4 patients who received this dose.

Cardiac output: The average resting cardiac index was not altered significantly by the administration of 160–200 μg/kg of practolol but was reduced from 2.4 to 2.1 liters/min per m² ($P < 0.01$) by the administration of 400 μg/kg and from 3.0 to 2.6 liters/min per m² ($P < 0.01$) by the administration of 600 μg/kg (Fig. 2). Although the average maximal cardiac index achieved during supine exercise was slightly lower after administration of 200 and 400 μg/kg of practolol, these reductions

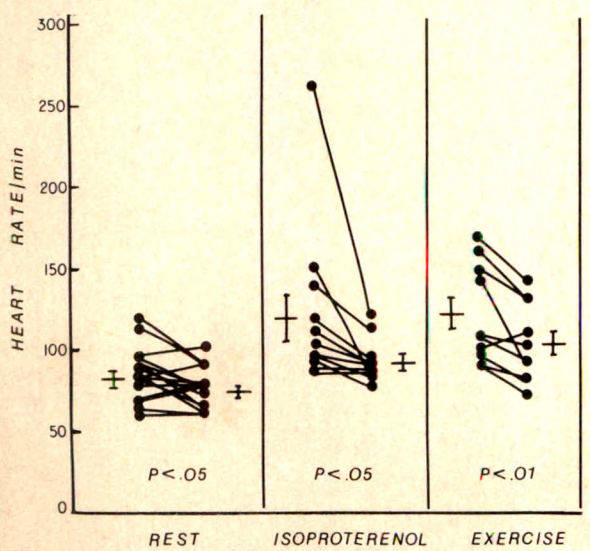

Figure 1. Effect of practolol on heart rate at rest, in response to isoproterenol and during exercise in patients receiving 400 or 600 μg/kg. Crossed I bar indicates mean ± standard error of the mean. In this and other figures, data to the left represent control data, and to the right, the value measured after the administration of practolol.

TABLE II

Hemodynamic Indexes at Rest and During Exercise Before and After Practolol

	Rest		Exercise	
	Control	Practolol	Control	Practolol
RA M	5.2 ± 2.1	5.8 ± 2.4	7.7 ± 3.5	9.3 ± 4.7
PAW M	18.3 ± 7.1	17.6 ± 6.6	24.5 ± 10.1	22.9 ± 7.7
PA M	26.8 ± 9.3	25.6 ± 8.0	40.3 ± 17.4	40.3 ± 15.3
LVed	11.6 ± 5.0	11.6 ± 7.1	16.0 ± 8.1	14.1 ± 9.0
Ao M	91.8 ± 14.5	89.9 ± 12.3	100.1 ± 16.2	94.3 ± 15.7
SI	34.0 ± 10.0	33.0 ± 11.0	34.0 ± 12.0	35.0 ± 13.0
PVR	2.1 ± 1.0	1.9 ± 1.3	1.9 ± 1.2	2.5 ± 2.1
SVR	19.8 ± 5.4	21.5 ± 6.4	16.9 ± 6.3	17.9 ± 5.7
a-v $O_2\Delta$	5.4 ± 1.1	5.8 ± 1.3	9.9 ± 3.1	10.8 ± 3.7
SW	71.8 ± 21.0	66.5 ± 19.0	62.8 ± 18.0	61.7 ± 10.0

All values presented are averages ± standard errors. Differences were not significant in any index at rest or during exercise.

SW = stroke work (g-m); other abbreviations as in Table I.

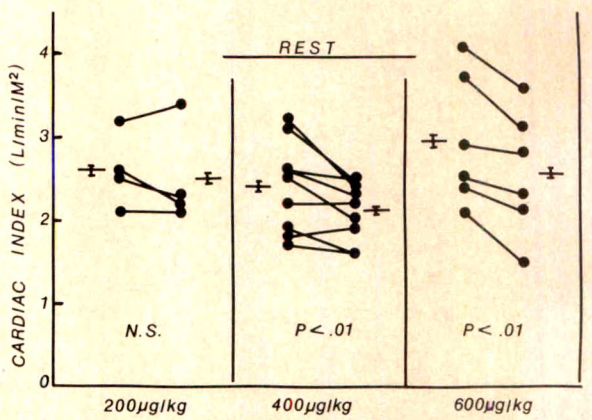

Figure 2. Effects of 3 levels of practolol on resting cardiac index. N.S. = not significant.

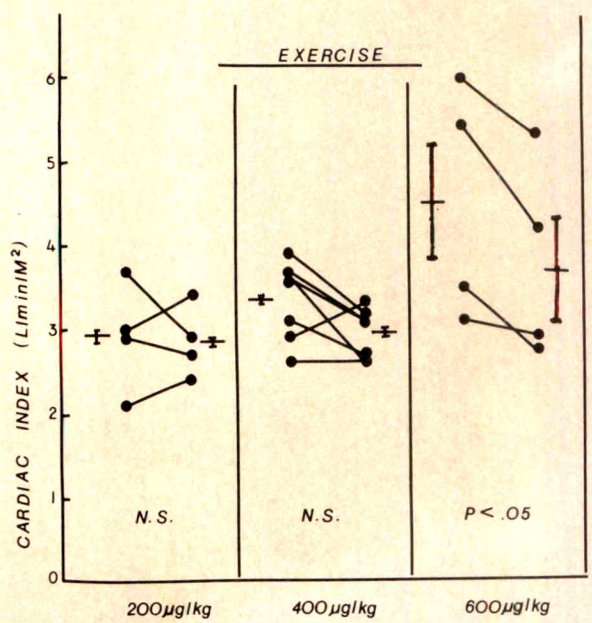

Figure 3. Effects of 3 levels of practolol on cardiac index during exercise.

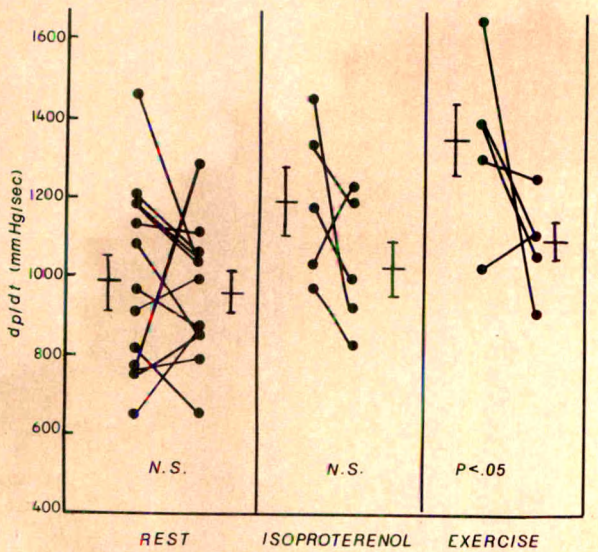

Figure 4. Effects of 400 and 600 μg/kg of practolol on the rate of pressure development in the left ventricle (LV dp/dt) in 3 conditions.

were not statistically significant (Fig. 3). However, after administration of 600 μg/kg of practolol, the maximal cardiac index achieved during exercise was decreased by 16 percent, an average of 4.5 to 3.8 liters/min per m^2, which was significant ($P < 0.05$) (Fig. 3).

When the patients with mitral stenosis are presented separately from those with diseases affecting the left ventricle, the action of the drug is shown to be more pronounced. Patients with mitral stenosis had no significant reduction in cardiac output after administration of practolol, but the

TABLE III

Cardiac Output (liters/min) Before and After Practolol

	REST		
	Control	Practolol	P Value
All patients (no. = 21)	4.6 ± 3	4.3 ± 3	0.05
Mitral stenosis (no. = 14)	4.2 ± 3	3.9 ± 3	NS
Left ventricular disease (no. = 7)	5.4 ± 5	4.5 ± 5	0.01

NS = not significant.

decrease was significant in those with left ventricular disease (Table I). When both groups are presented together, the findings show at all dose ranges a small but significant decrease in cardiac output in response to administration of practolol (Table III).

Left ventricular dp/dt: The effects of practolol, 400 and 600 μg/kg, on the average of left ventricular dp/dt were not significant at rest (Fig. 4). The increase in left ventricular dp/dt produced by injection of isoproterenol was also not significantly altered by higher doses of practolol, although only 5 patients were studied. The elevation of left ventricular dp/dt produced by exercise was slightly but significantly reduced from 1,348 to 1,085 mm Hg/sec ($P < 0.05$) after administration of the larger doses of practolol (Fig. 4). Low doses of practolol (160 or 200 μg/kg) had no effect on left

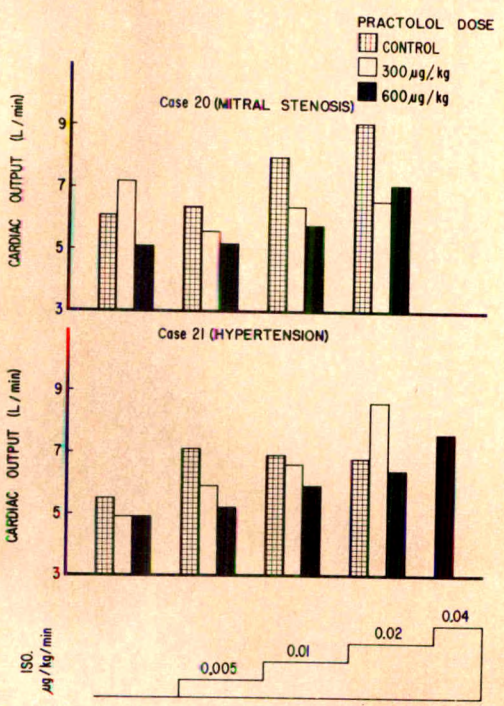

Figure 5. Cardiac output determinations in 2 patients receiving successive, increasing doses of practolol and isoproterenol.

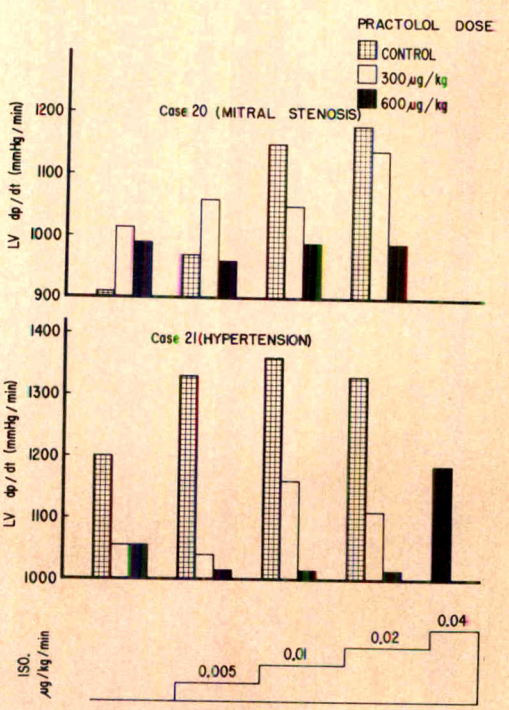

Figure 6. Left ventricular dp/dt in 2 patients receiving successive doses of practolol and isoproterenol.

ventricular dp/dt at rest, during exercise or after injection of isoproterenol.

Effect of isoproterenol: Figure 5 illustrates the increments in cardiac output in response to graded infusion of isoproterenol during a control period and after administration of 300 and 600 μg/kg of practolol in 2 patients. The dose response curves were shifted to the right and downward following both levels of practolol; that is, there was less increase in cardiac index for a given dose of isoproterenol. Similar observations were made in respect to increments of left ventricular dp/dt produced by isoproterenol after administration of practolol (Fig. 6). The other hemodynamic data on these patients are presented in Table IV.

Other hemodynamic changes: No consistent or significant changes in right atrial, pulmonary arterial, pulmonary arterial wedge, left ventricular end-diastolic, or arterial pressures were noted after any of the 3 levels of practolol administration. Neither systemic nor pulmonary vascular resistance was altered by the drug. Stroke index and stroke work were not significantly reduced by the administration of practolol (Tables I, II and IV).

Side effects: Although several transient side effects were noted during and after administration of practolol, none was serious enough to merit treatment. The side effects were not dose-related. Two patients complained of brief nausea after receiving the drug. In 2 patients atrial fibrillation developed during manipulation of the catheter in the right atrium, in 1 before and in 1 after beta blockade. In both there was reversion to sinus rhythm within 24 hours. In another patient transient nodal rhythm developed during the catheterization after administration of practolol but reverted to sinus rhythm within 3 hours.

Discussion

Our studies were designed to evaluate the overall circulatory effects of practolol in patients with various forms of heart disease, and to attempt to assess its beta blocking activity in relation to its propensity to depress cardiac function.

In the resting state, only minimal changes in circulatory dynamics were observed after the administration of 160 to 600 μg/kg of practolol. In spite of the relative depression of cardiac output

TABLE IV

Hemodynamic Responses to Graded Levels of Isoproterenol and Various Doses of Practolol in 2 Patients

Pract	Iso	RA	RV S/ED	PA S/D/M	PAW	LV S/ED	Ao S/D/M	HR	CO	CI	SV	SI	SWI	dp/dt
A. Case 20 (Mitral Stenosis, Sinus Rhythm)														
0	0	7	47/8	44/20/28	24	110/10	116/74/95	96	6.1	3.7	65	39	50.4	910
	0.005	6	47/8	49/30/34	...	112/6	112/72/90	170	6.4	3.9	38	23	28.2	975
	0.010	7	63/7	62/28/47	...	104/6	104/70/84	210	8.0	4.8	38	23	26.3	1,150
	0.020	7	80/10	75/37/52	...	110/6	110/66/81	260	9.0	5.4	35	21	23.1	1,175
300	0	7	52/4	52/31/40	...	116/6	116/82/100	96	7.2	4.2	75	45	61.2	1,012
	0.005	9	48/4	47/32/35	...	110/8	110/74/84	102	5.8	3.5	56	34	38.8	1,063
	0.010	7	53/–	56/33/44	...	102/8	102/66/76	108	6.4	3.9	60	36	37.2	...
	0.020	8	69/–	69/37/49	...	106/6	106/66/78	122	6.6	4.0	55	33	35.0	1,139
600	0	8	45/4	44/28/35	...	110/8	110/80/86	102	5.1	3.1	50	30	35.1	987
	0.005	7	48/5	49/32/39	...	104/6	104/72/82	108	5.2	3.1	48	29	32.3	962
	0.010	8	54/–	54/30/42	...	108/8	108/68/78	108	5.8	3.5	53	32	33.9	987
	0.020	6	54/3	58/32/43	...	92/8	92/66/74	126	7.0	4.2	55	33	33.2	987
B. Case 21 (Hypertension, Sinus Rhythm)														
0	0	...	...	...	...	164/10	180/96/130	84	5.5	2.5	65	30	53.0	1,200
	0.005	...	...	37/15/23	...	180/9	180/94/123	96	7.1	3.3	74	34	56.9	1,333
	0.010	...	...	39/17/24	...	168/6	168/86/113	100	6.9	3.2	70	32	49.2	1,358
	0.020	...	...	40/15/23	...	150/4	150/72/100	112	6.8	3.1	61	28	38.1	1,333
300	0	2	37/5	39/17/22	12	174/22	174/100/120	80	4.9	2.3	63	29	47.3	1,061
	0.005	...	...	38/17/25	...	156/10	156/86/116	84	5.8	2.7	70	32	50.5	1,037
	0.010	...	...	39/18/26	...	170/14	170/88/118	92	6.7	3.1	76	35	56.2	1,160
	0.020	...	...	39/17/22	...	146/8	146/78/96	104	8.6	4.0	83	38	49.6	1,111
600	0	5	37/5	42/21/28	15	168/28	168/96/116	80	4.9	2.3	63	29	45.8	1,061
	0.005	...	...	40/17/29	...	159/11	159/100/114	84	5.6	2.4	63	29	45.0	1,012
	0.010	...	...	36/15/21	...	136/8	141/76/108	86	5.9	2.7	67	31	45.5	1,012
	0.020	...	...	38/14/22	...	150/7	150/82/98	92	6.4	2.9	70	32	42.7	1,012
	0.040	...	...	45/19/23	...	140/7	140/76/94	112	7.5	3.5	67	31	39.6	1,135

Iso = dose of isoproterenol in μg/kg per min. Other abbreviations as in Table I.

and elevation of end-diastolic pressure levels in the patients with more severe degrees of circulatory impairment in the control period, no further significant increase in left ventricular end-diastolic pressure was noted, even after the higher doses of practolol were administered (Table II). (This was true of patients with mitral stenosis as well as those with conditions affecting the left ventricle.) Furthermore, at rest left ventricular dp/dt did not fall significantly, despite a decrease in heart rate and a small decrease in the cardiac index. These observations are especially important, since they were made after the administration of doses of practolol which produced substantial beta adrenergic blockade as demonstrated by the responses to isoproterenol challenges. All of these observations suggest that practolol has little negative inotropic effect in the doses administered in these patients at rest.

In low doses the drug appeared to augment the contractile state of the heart. In Patient 20, with mitral stenosis, the drug augmented cardiac output at the 300 μg/kg level and increased left ventricular dp/dt at both the 300 and 600 μg/kg levels (Table IV). Other investigators have noted this beta stimulating effect of the drug.[7]

Practolol altered the circulatory responses to exercise only slightly. The maximal heart rate, left ventricular dp/dt and cardiac index achieved during exercise were reduced significantly after administration of 600 μg/kg of practolol, but not altered by the administration of 400 μg/kg. No other hemodynamic changes occurring during supine exercise were significantly different after the administration of practolol from those recorded during the control exercise study (Table II). No difference in the responses of cardiac output to exercise, either before or after practolol, was noted when the patients with left ventricular disease were presented separately from those with mitral stenosis. The supine posture undoubtedly modified the effects produced by the drug, since adrenergic status is more important in the erect posture.

Significant beta adrenergic blockade was demonstrated by a dose of 300 to 400 μg/kg in this study and documented by blockade of the effects of exogenously administered isoproterenol. A dose of 600 μg/kg of practolol did not appear to be significantly more effective in producing beta adrenergic blockade than the dose of 400 μg/kg, when comparative studies were made utilizing single doses of practolol in patients given each dose level. However, when dose response curves were performed, as in Cases 20 and 21, practolol in doses of 300 and 600 μg/kg produced stepwise and significantly different levels of blockade to infusions of isoproterenol (Fig. 5). The dose-response curves were shifted downward and to the right in a progressive fashion, as would be expected when a competitive antagonist was used to block the adrenergic receptors.

Clinical implications: Although the data neither confirm nor negate the contention of Sowton et al.[8] that the drug has more negative chronotropic than negative inotropic effects, it does seem that effective beta blockade can be induced with practolol at levels that do not significantly impair ventricular performance. However, it should be emphasized that the condition of any patient who is dependent upon his sympathetic nervous system to maintain circulatory compensation may deteriorate following beta blockade.

Practolol produced little impairment of circulatory function when given to patients with either left ventricular disease or mitral stenosis in the resting state. The drug does not markedly impair circulatory performance during exercise, although at higher doses the cardiac index was lower than in the control conditions. These changes appear to be directly related to the slower heart rate that the drug produced. Only at higher doses and during exercise did practolol significantly alter the rate at which left ventricular tension was developed during exercise, and dose-response curves to isoproterenol progressively were shifted to the right and downward by the administration of practolol in progressively larger doses. These altered hemodynamics appeared to be more prominent in patients with left ventricular disease but are still of minor consequence.

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Evaluation of Left Ventricular Function from Isovolumic Pressure Measurements During Isometric Exercise

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In 24 patients left ventricular (tipmanometer) and aortic pressure measurements were carried out before and during a standardized handgrip. On the basis of findings at diagnostic cardiac catheterization, the patients were divided into 2 groups. Group 1 consisted of 13 patients without or with minimal loading of the left ventricle; group 2 comprised 11 patients with a primarily pressure-loaded left ventricle or coronary heart disease. During handgrip left ventricular systolic pressure, end-diastolic pressure and heart rate increased significantly in both groups. However, the extent of the increase of left ventricular end-diastolic pressure was considerably greater in group 2 (+8.2 mm Hg) than in group 1 (+2.0 mm Hg). Both left ventricular maximal dP/dt and the maximal quotient (dP/dt)/P, which represents a measure of the velocity of shortening of the contractile elements, increased significantly in group 1; in group 2 only maximal dP/dt increased significantly, and this increase was only about half of that observed in group 1. The time intervals from the onset of contraction to the points of maximal dP/dt and maximal (dP/dt)/P, respectively, shortened significantly during handgrip in group 1 and remained unchanged in group 2. We conclude that (1) left ventricular contractile function is impaired in patients in group 2 compared with that in group 1; (2) the primary response of the normal or near normal left ventricular myocardium to an acute load produced by handgrip is enhancement of the contractile state; and (3) the compromised left ventricular myocardium is most likely to utilize the Frank-Starling mechanism to generate increased pressure.

High-fidelity pressure measurements have been recently employed to assess left ventricular contractile function in man.[1–10] From the isovolumic portion of auxotonic beats pressure-velocity curves may be constructed that serve to determine the maximal velocity of the contractile elements (Vmax), the independent measure of contractility.[2–6,10,11] The Vmax of patients with myocardial hypertrophy secondary to chronic pressure overloading, and particularly of those with idiopathic myocardial disease, has been reported[4] to be significantly reduced compared with that of normal control subjects. However, another study[10] showed considerable overlap of Vmax in patients whose usual resting catheterization data suggested normal left ventricular function and in those who had abnormal cardiac function on the basis of decreased left ventricular ejection fraction or increased end-diastolic volume or pressure. Furthermore, estimation of Vmax by extrapolating pressure-velocity curves is often difficult and subjective in nature.[11–13]

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It is therefore anticipated that evaluation of contractile function may be facilitated if one relies primarily on changes in left ventricular dynamic values during an induced additional stress rather than during rest. Moreover, left ventricular contractile function can be assessed by the use of finitely measurable velocity indexes, such as the maximal rate of rise of left ventricular pressure[14] and the peak measured velocity of shortening of the contractile elements,[8,12,13,15–17] when due consideration is given to variations in loading occurring during stress.

A stress test that is particularly easy to perform at cardiac catheterization is isometric exercise.[18–23] We therefore chose a standardized handgrip test for the present study in which we intended to assess left ventricular function in 2 groups of patients (1) those without or with minimal loading of the left ventricle and (2) those with an essentially pressure-loaded left heart chamber or with coronary disease.

Material and Methods

Twenty-four patients were studied by right and left heart catheterization for diagnostic purposes. They were given Librium®, 10 mg orally, 1 hour before the procedure. After the diagnostic part of the catheterization a Statham SF-1 (23 cases) or a Telco (Gentilly) (1 case) tipmanometer catheter was introduced in 7 instances into the left ventricle through an atrial septal defect, in 2 instances through an open foramen ovale, in 4 instances by the retrograde aortic route[24] and in 11 instances by the transseptal approach.[25] Informed consent of the patients was obtained for this study. When the tipmanometer was positioned in the left ventricle 5,000 units of heparin was administered intravenously.

The 24 patients were divided into 2 groups according to the results of the diagnostic catheterization at rest. Group 1 comprised 13 patients without or with minimal loading of the left ventricle: 7 patients with uncomplicated atrial septal defect, 2 with patent ductus arteriosus (left to right shunt 11 and 18 percent, respectively, of the pulmonary flow), 1 with moderate valvular pulmonary stenosis and open foramen ovale, 1 with minimal coarctation of the aorta (4 mm Hg difference between mean pressures in the ascending and descending aorta), 1 with moderate primary pulmonary hypertension and open foramen ovale and 1 with pectus excavatum. Group 2 comprised 11 patients. Four had aortic stenosis and mild aortic incompetence (mean systolic pressure gradient across the aortic valve between 62 and 90 mm Hg; aortic regurgitant fraction as determined by thermodilution[26] less than 0.13). In 1 of these 4 patients minimal mitral regurgitation was detected by left ventricular angiocardiography; in another, a small ventricular septal defect with a left to right shunt of 20 percent of the pulmonary flow was present. Two patients had combined aortic valve stenosis and incompetence (mean systolic pressure gradient across the aortic valve 17 and 27 mm Hg, aortic regurgitant fraction 0.35 and 0.40, respectively). Four patients had coronary heart disease in which selective coronary arteriography,[27] performed after the handgrip study, revealed either complete or almost complete occlusion of at least 1 of the 3 major coronary vessels. In 3 of these 4 patients there was electrocardiographic evidence of earlier myocardial infarction, and the fourth patient presented typical angina after walking 20 Master steps and had signs of ischemia in the electrocardiogram. The eleventh patient had idiopathic biventricular hypertrophy of the myocardium.

All patients had sinus rhythm at the time of the study except 2 with atrial septal defect who had nodal rhythm. The electrocardiogram of 1 patient with atrial septal defect showed right bundle branch block (QRS interval 0.14 second), and that of 1 patient with combined aortic stenosis and incompetence showed left bundle branch block (QRS interval 0.14 second). In the remaining patients the duration of the QRS interval ranged from 0.07 to 0.11 second.

The following hemodynamic variables were determined: left ventricular pressure (P) by the tipmanometer and through the lumen of the catheter by the conventional technique (external Statham P23Db pressure transducer); aortic pressure by the conventional technique and in some cases by a Statham SF-1 tipmanometer catheter; heart rate; and electrocardiogram. From the high-fidelity left ventricular pressure curves the first derivative (dP/dt) and the instantaneous quotient (dP/dt)/P were obtained by an analog calculating unit.[13,25] All recordings were made on an Electronics for Medicine DR/8 oscillograph at a paper speed of 200 mm/sec.

From the pressure recordings the following measurements were made: left ventricular peak systolic, left ventricular end-diastolic, systolic aortic, diastolic aortic and mean aortic pressures, maximal rate of rise of left ventricular pressure (maximal dP/dt), time interval from the onset of contraction to the point of maximal dP/dt (t-dP/dt), maximal quotient (dP/dt)/P, time interval from the onset of contraction to the point of maximal (dP/dt)/P (t − max[dP/dt]/P), time interval from the onset of contraction to the point of aortic valve opening (t-isov). The measurements were carried out in those beats with a left ventricular end-diastolic pressure that represented an average value of all beats over 1 respiratory cycle.

When a constant left ventricular geometry is assumed during the isovolumic portion of contraction and when there is a normal spread of activation, (dP/dt)/P is proportional to the velocity of shortening of the contractile elements (V_{CE}).[6,10,11] By inserting the coefficient of series elasticity into the denominator, V_{CE} can be calculated in terms of muscle lengths or circumferences/sec.[6,10] Although in cat papillary muscles a similar coefficient of series elasticity has been reported for the normal, hypertrophied and failing myocardium,[28] the assumption of a uniform coefficient in the present study with patients having coronary heart disease did not appear to be justified. Forwand et al.[29] showed that in dogs with chronic myocardial infarction from ligation of the left anterior descending coronary artery the coefficient of series elasticity was only about half of that determined in dogs with normal left ventricular myocardium. Therefore, no calculation of V_{CE} in terms of muscle lengths or circumferences/sec was attempted. However, in a given patient the value of maximal (dP/dt)/P computed during the isovolumic phase of contraction provides a valid index for changes of peak measured velocity of shortening during handgrip.

It is clear that in contrast to the extrapolated Vmax peak measured velocity cannot be considered an independent measure of contractility because it would be influenced somewhat by variations in preload. In the 2 patients with bundle branch block maximal (dP/dt)/P was not determined since, in the presence of asynchronous activation, local fiber shortening and stretching is likely to occur during the early part of isovolumic contraction, resulting in different preloads in the various parts of the left ventricular myocardium. Although Vmax at zero load can be expected not to be altered by asynchronous activation,[30] changes of peak measured velocity may well occur due to altered overall preload. In 1 patient with atrial septal defect in group 1, the curve of the quotient (dP/dt)/P was not satisfactory for technical reasons and was discarded.

In 2 patients in group 2 with minimal mitral incompetence and a small ventricular septal defect no true isovolumic portion of the left ventricular systole was present. However, the data in these 2 cases were included in the calculations of maximal dP/dt and maximal (dP/dt)/P because (1) the escape of blood from the left ventricular end-diastolic volume through the mitral valve and the ventricular septal defect, respectively, during the time interval from the onset of contraction to the moment of aortic valve opening, and therefore left ventricular fiber shortening, was presumably small, and (2) the major emphasis in this study was on the magnitude of change of the left ventricular velocity indexes during handgrip rather than on comparison between control values.

The experimental protocol for the handgrip test was as follows: The patient was first familiarized with a balloon dynamometer (Fig. 1) that he had to squeeze with the right hand. This dynamometer consists of a water-filled rubber balloon (diameter 5.5 cm) to which a vertical closed-tip glass tube is attached. The pressure developed within the balloon during compression is indicated by the height of the level to which the fluid rises. The pressure in kg/cm^2 is read from a nonlinear scale attached to the glass tube. The performance achieved during a compression time of 1 to 2 minutes ranged from 0.2 to 0.4 kg/cm^2. When the patient had become familiar with the handgrip test, a control run at rest was carried out. He was then asked to squeeze the balloon with an intensity that, according to his constitution, he could presumably hold during 2 minutes. Experimental runs were obtained after 1 and 2 minutes of compression. When the patient was able to hold the same level of compression for 2 minutes the experimental run after 2 minutes was used for calculations. When he could not maintain the initial level between the first and the second minutes, calculations referred to the run obtained after the first minute. To eliminate an intrathoracic increase in pressure by an eventual Valsalva maneuver the patient was asked to speak during the few instances of pressure recording. The average handgrip performance in the 2 groups was quite similar (0.30 ± 0.05 [SD] kg/cm^2 in group 1 and 0.31 ± 0.04 kg/cm^2 in group 2).

Results

Group 1: Figure 2 illustrates the hemodynamic changes that occurred during handgrip in a patient representative of group 1. Isometric exercise led to an increase in heart rate, left ventricular peak systolic pressure, and systolic, diastolic and mean aortic pressures. Left ventricular end-diastolic pressure increased slightly. Maximal dP/dt and maximal (dP/dt)/P increased, and the time intervals from the onset of contraction to these 2 points shortened (Table I). All variables changed significantly except the time interval from onset of contraction to aortic valve opening. The increase of left ventricular end-diastolic pressure although significant was slight (+2 mm Hg). On the average, maximal dP/dt during control occurred 8 msec (range 0 to 16 msec) and during handgrip 11 msec (range 4 to 23 msec) before aortic valve opening.

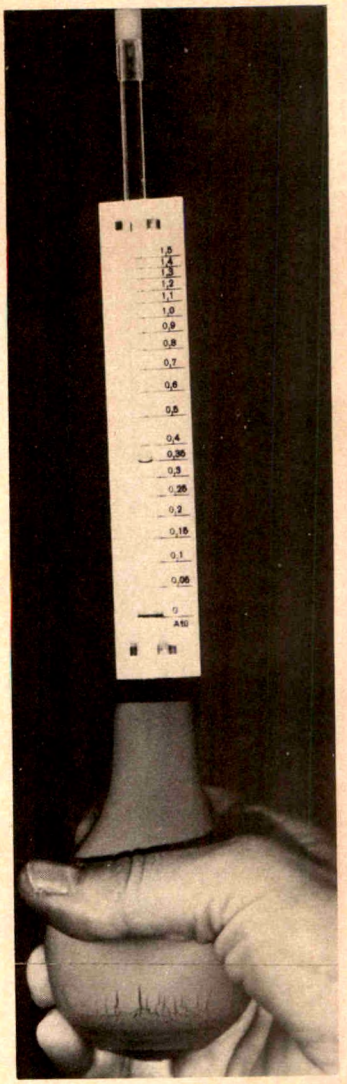

Figure 1. Balloon dynamometer that allows standardized handgrip studies.

Group 2: Figure 3 shows the hemodynamic effects of handgrip in a single experiment. As in group 1, a definite increase in heart rate, left ventricular peak systolic pressure and systolic, diastolic and mean aortic pressures occurred. Left ventricular end-diastolic pressure increased sizably. There was also an increase of maximal dP/dt. Maximal (dP/dt)/P decreased slightly. The time

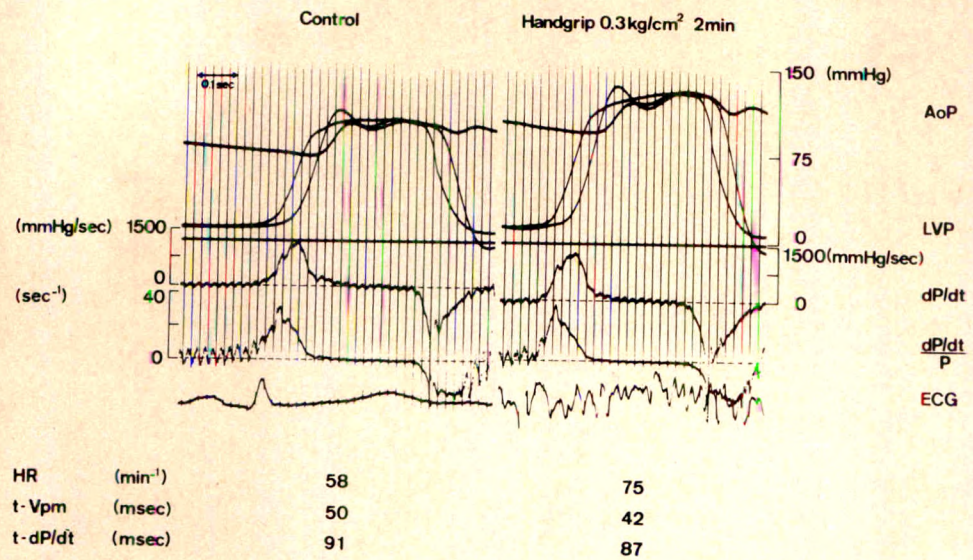

Figure 2. Isometric exercise by handgrip in a patient from group 1 with an atrial septal defect. During handgrip the left ventricular systolic pressure, the aortic pressure and the heart rate increased. The left ventricular end-diastolic pressure increased slightly. Maximal dP/dt and the maximal quotient (dP/dt)/P tended to increase. The time intervals t-Vpm and t-dP/dt shortened. The left ventricular pressure is measured by a Statham SF-1 tipmanometer and by the conventional technique. During handgrip the electrocardiogram is distorted by artifacts due to muscle contractions. AoP = aortic pressure; dP/dt = rate of rise of left ventricular pressure (first derivative); dP/dt/P = instantaneous quotient of first derivative divided by left ventricular pressure; ECG = electrocardiogram; HR = heart rate; LVP = left ventricular pressure; t-dP/dt = time interval from the onset of contraction to the point of maximal dP/dt; t-Vpm = time to peak velocity, that is, time interval from the onset of contraction to the point of maximal (dP/dt)/P.

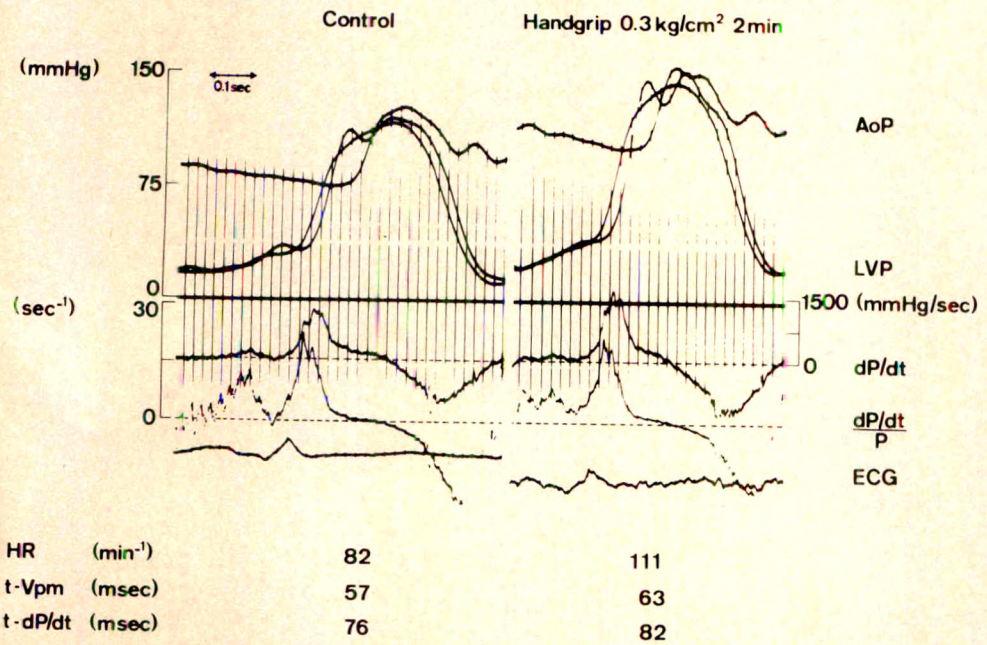

Figure 3. Isometric exercise by handgrip in a patient from group 2 with coronary heart disease. Similar to the effects in the patient from group 1, handgrip led to an increase of the left ventricular systolic pressure, the aortic pressure and the heart rate. In contrast, the left ventricular end-diastolic pressure showed a more pronounced increase than in the patient from group 1 depicted in Figure 2. Whereas maximal dP/dt increased, maximal (dP/dt)/P tended to decrease during handgrip. The time intervals t-Vpm and t-dP/dt lengthened slightly. The left ventricular pressure is measured by a tipmanometer and by the conventional technique. Abbreviations as in Figure 2.

intervals from the onset of contraction to the points of maximal dP/dt and maximal (dP/dt)/P tended to increase under isometric exercise.

Table I shows the pooled data of group 2 and the differences in changes of the various indexes studied in the 2 groups. Heart rate, left ventricular peak systolic pressure and systolic, diastolic and mean aortic pressures increased significantly; the extent of increase was similar to that in group 1. Left ventricular end-diastolic pressure also increased significantly; however, the magnitude of increase (+8.2 mm Hg) was significantly greater than in group 1. Maximal dP/dt increased significantly. In the control state maximal dP/dt occurred 3 to 16 msec before aortic valve opening except in 3 patients with predominant aortic stenosis whose maximal dP/dt fell into the early portion of the ejection phase (4, 18 and 36 msec, respectively, after aortic valve opening). In 2 of these 3 patients maximal dP/dt occurred slightly within the early ejection phase, even when diastolic aortic pressure had increased during handgrip. Maximal (dP/

TABLE I

Left Ventricular Dynamics During Handgrip (mean values ±1 SD)

	Age (yr)	LVSP (mm Hg)	LVEDP (mm Hg)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	HR (per min^{-1})	max dP/dt (mm Hg/sec)	max $\frac{dP/dt}{P}$ (sec^{-1})	t-dP/dt (msec)	t-max $\frac{dP/dt}{P}$ (msec)	t-isov (msec)
Group 1 (9 Women, 4 Men)												
Control	31.1 ±14.6	111 ±13	10.6 ±3.8	111 ±13	70 ±6	90 ±9	74 ±20	1540 ±350	39.1 ±8.2	72 ±13	43 ±10	80 ±15
Handgrip (0.30 ± 0.05 kg/cm²)		138 ±21	12.6 ±4.1	138 ±21	89 ±11	112 ±14	95 ±21	2100 ±870	46.5 ±9.6	66 ±11	37 ±6	77 ±14
no.		13	13	13	13	13	13	13	11	13	11	
P value*		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.01	<0.02	<0.05	NS
Group 2 (2 Women, 9 Men)												
Control	45.5 ±11.0	166 ±50	22.7 ±8.5	127 ±20	73 ±8	96 ±10	73 ±9	1560 ±470	30.4 ±11.1	70 ±14	40 ±12	72 ±18
Handgrip (0.31 ± 0.04 kg/cm²)		190 ±51	30.9 ±9.5	155 ±23	92 ±13	119 ±14	91 ±13	1830 ±460	27.8 ±9.2	68 ±11	42 ±11	70 ±15
no.		11	11	11	11	11	11	11	10	11	10	11
P value*		<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	NS	NS	NS	NS
P value†		NS	<0.01	NS	NS	NS	NS	NS	<0.01	NS	<0.05	NS

* Determined by paired t test.

† Determined by unpaired t test; values refer to the differences in changes of all the variables observed in the 2 groups.

DAP = diastolic aortic pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular peak systolic pressure; MAP = mean aortic pressure; max dP/dt = maximal rate of left ventricular pressure rise; max $\frac{dP/dt}{P}$ = maximal quotient of dP/dt divided by P during isovolumic contraction; no. = number of observations; NS = not significant ($P > 0.05$); SAP = systolic aortic pressure; t-dP/dt = time interval from the onset of contraction to the point of max dP/dt; t-isov = duration of the isovolumic contraction; t-max $\frac{dP/dt}{P}$ = time interval from the onset of contraction to the point of max $\frac{dP/dt}{P}$.

dt)/P showed only minor and insignificant changes during isometric exercise. Comparison with the changes of this index in group 1 showed a statistically significant difference. The time intervals from the onset of contraction to the points of maximal dP/dt and maximal (dP/dt)/P remained essentially unchanged during handgrip. As in group 1, the duration of isovolumic contraction did not change significantly.

Discussion

It is generally accepted that, in contrast to dynamic exercise, isometric exercise such as that performed during handgrip leads to a sizable increase in aortic pressure and thus constitutes an acute pressure load of the left ventricle.[18–23] Several investigators[20–23] have used handgrip to stress the heart during catheterization. In their studies[21,22] left ventricular function was evaluated from the changes of external performance of the left heart chamber, that is, the variations of stroke work, relative to changes in left ventricular end-diastolic pressure. However, we know of no investigation in which left ventricular function was assessed by velocity indexes derived from the isovolumic portion of high-fidelity left ventricular pressure curves.

Myocardial contractility in response to handgrip: The response to standardized handgrip of our patients whose findings at catheterization showed no or minimal loading of the left ventricle (group 1) was characterized by a significant increase of maximal dP/dt (Table I) associated with a significant increase in left ventricular end-diastolic pressure that in absolute terms was small (average +2.0 mm Hg). Figure 4 illustrates the changes that took place in the individual patients in group 1. In group 2, comprising patients with a primarily pressure-loaded left ventricle or coronary heart disease, there was also a significant increase of maximal dP/dt although it was only about half of the magnitude observed in group 1. This increase in maximal dP/dt was accompanied by a large augmentation of left ventricular end-diastolic pressure. Therefore, the individual "ventricular function curves" (Fig. 4) showed in general a flatter slope in patients in group 2 than in patients in group 1. Hence, left ventricular contractile function appeared to be impaired in the majority of patients in group 2. The patient in this group who showed at rest the lowest value for

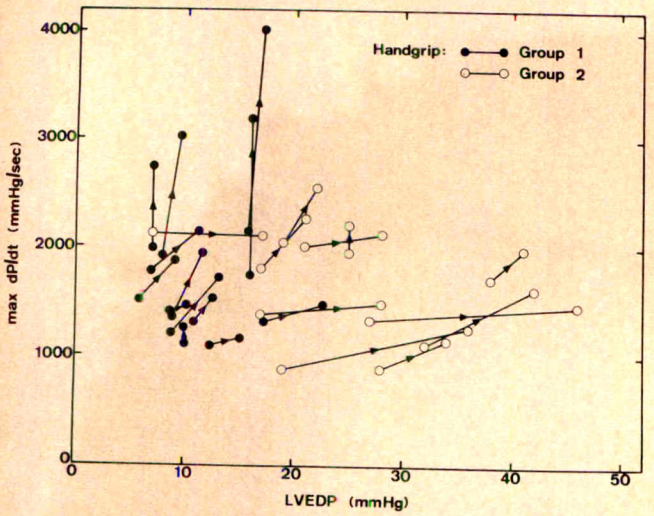

Figure 4. Changes of the maximal rate of rise of left ventricular pressure (max dP/dt) and of the left ventricular end-diastolic pressure (LVEDP) during handgrip in the individual patients. One may note that in the majority of the patients of group 1 the slope of the "ventricular function curves" was steeper than in the patients of group 2. The flattened slope of the patients in group 2 is indicative of a reduced left ventricular contractility as compared to the cases in group 1.

left ventricular end-diastolic pressure (less than 10 mm Hg) and the highest maximal dP/dt (more than 2,000 mm Hg/sec) had a clearly pathologic response to handgrip: maximal dP/dt remained unchanged during isometric exercise, whereas left ventricular end-diastolic pressure increased 10 mm Hg.

A different response to handgrip of the 2 groups of patients was also observed when maximal (dP/dt)/P was plotted against left ventricular end-diastolic pressure (Fig. 5). In group 1 all but 1 patient had an increase in maximal (dP/dt)/P associated with no change or small increases in left ventricular end-diastolic pressure. In contrast the response of maximal (dP/dt)/P in the patients of group 2 was variable with a tendency toward a decrease. Since left ventricular end-diastolic pressure increased sizably in the majority of patients in group 2 the course of the "ventricular function curves" in this group was very flat or even descending, whereas more or less steeply ascending curves were elicited by patients in group 1 (Fig. 5).

Maximal dP/dt, maximal (dP/dt)/P and left ventricular afterload and preload: The use of maximal dP/dt and maximal (dP/dt)/P as indexes for the assessment of left ventricular contractile function needs some comment. In animals[31–33] and in man[14,24,34] it has been shown that maximal dP/dt is dependent not only on myocardial contractility but also on afterload and preload. An increase in afterload as well as in preload leads to an increase in maximal dP/dt. With respect to the afterload dependency, it must be mentioned that in dogs an increase in maximal dP/dt was observed when, before an enhancement of diastolic aortic pressure, maximal dP/dt occurred simultaneously or not more than 5 msec before aortic valve opening.[32] An increase of maximal dP/dt can also be expected after an augmentation of diastolic pressure when, in the control state at low diastolic pressure, maximal dP/dt falls into the early part of the ejection phase.[32] If the same afterload dependency applies to the human left ventricle, one would expect that the significant increase of maximal dP/dt observed during handgrip was partially due to the enhancement of diastolic aortic pressure. This would be especially true in group 2 in which in 3 patients at rest maximal dP/dt occurred after aortic valve opening and in 2 patients it occurred 3 and 4 msec before aortic valve opening. The same mechanism must also be invoked in 3 of 11 cases in group 1; maximal dP/dt at rest occurred in 2 instances at the time of aortic valve opening and in 1 instance 4 msec before this time.

With respect to the preload dependency of maximal dP/dt the following considerations may be made: If one accepts that the extent of increase in left ventricular end-diastolic pressure that occurred during handgrip represents most likely an increase in preload, one may suspect that the contribution of preload to the enhancement of maximal dP/dt was probably greater in group 2 than in group 1. It is recognized, however, that the real determinants of preload are end-diastolic fiber length or end-diastolic stress. Since left ventricular end-diastolic volume was not measured in this study we do not know if these indexes actually increased more in group 2 than in group 1.

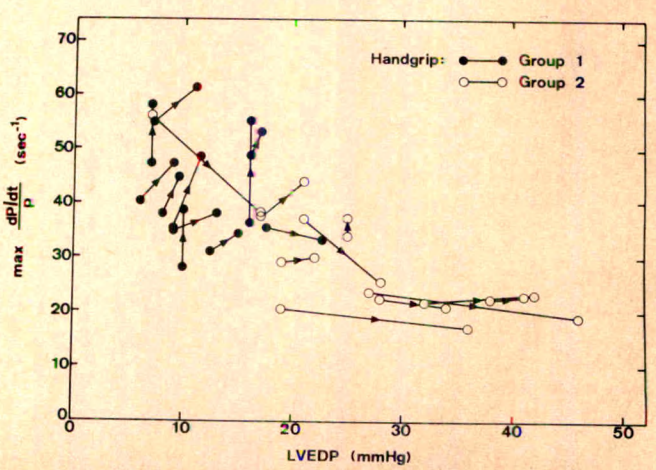

Figure 5. Changes of the maximal quotient (dP/dt)/P and of the left ventricular end-diastolic pressure (LVEDP) during handgrip in the individual patients. There is a clearly different response to handgrip in the 2 groups. Whereas in group 1 all but 1 patient elicited an increase of maximal (dP/dt)/P with no change or a small increase of left ventricular end-diastolic pressure, maximal (dP/dt)/P in group 2 showed a variable response with some tendency to decrease that was associated with a sizable increase of left ventricular end-diastolic pressure in most cases.

When all the arguments about the possible influences of afterload and preload changes on maximal dP/dt during handgrip are summarized it can be said that the effects of the physical factors were probably less important in group 1 than in group 2. Since the increase of maximal dP/dt in group 1 was greater than in group 2 it appears reasonable to conclude that at least in group 1 an augmentation of contractility took place during isometric exercise, whereas in group 2 the variations of the physical determinants of maximal dP/dt may have been sufficient to explain its observed increase.

These conclusions are further supported by the changes of maximal (dP/dt)/P. Since maximal (dP/dt)/P occurs early in the isovolumic portion of left ventricular systole it is not likely that diastolic aortic pressure per se influences its magnitude. On the other hand it has been shown in animals[13,15] and in man[24] that maximal (dP/dt)/P depends on preload, that is, an increase in preload leads to a fall of maximal (dP/dt)/P. Since in group 1 the small increase in left ventricular enddiastolic pressure was associated with a significant increase of maximal (dP/dt)/P an augmentation of left ventricular contractility must be postulated. In group 2 maximal (dP/dt)/P tended to decrease during isometric exercise. This reaction is compatible with the view that no major change in contractility occurred during handgrip in group 2.

Additional insight into the behavior of contractility during handgrip was obtained from the time intervals from the onset of contraction to the point of maximal dP/dt and maximal (dP/dt)/P, respectively. In contrast to maximal dP/dt and maximal (dP/dt)/P these time intervals are practically uninfluenced by variations in preload.[13,32,34] In group 1 the time intervals shortened significantly during handgrip. This indicates that an increase of left ventricular contractility occurred. On the other hand, there was no change in the duration of the time intervals in group 2. This finding supports the aforementioned contention that left ventricular contractile state did not change.

Mechanisms of augmentation of myocardial contractility: The mechanisms by which myocardial contractility is augmented in patients with a normal or minimally loaded left heart chamber during handgrip are not clearly understood. It is most likely that with the prevalent increase in cardiac chronotropism there was an associated increase in sympathetic outflow to the myocardium. Both mechanisms are additive with respect to the observed enhancement of the inotropic state. It may be that the patients who had a diseased left ventricle did not increase their inotropic state during handgrip because the diseased myocardium is less responsive to sympathetic stimulation than the normal one.[35] Then, the Frank-Starling mechanism has to be mobilized to overcome the acute pressure burden induced by handgrip.

Acknowledgments

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Cardiac Arrhythmias Observed During Maximal Treadmill Exercise Testing in Clinically Normal Men

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The incidence of cardiac arrhythmias observed during maximal treadmill exercise testing was studied in 650 men aged 25 to 54 years. In 561 there was no clinical evidence of cardiovascular disease; 89 were classified as having definite or suspected cardiovascular disease. The patients were divided into 3 age groups—25 to 34, 35 to 44 and 45 to 54 years—to define any age-related differences in the incidence of arrhythmias during exercise. Single or consecutive ventricular premature complexes were observed in 31 percent of the 25 to 34 year olds, 38 percent of the 35 to 44 year olds and 49 percent of the 45 to 54 year olds; the incidence of supraventricular premature complexes was 7, 10 and 14 percent, respectively. The incidence of both ventricular and supraventricular complexes increased with age. For any given age group the incidence of ventricular premature complexes was greater in patients with definite or suspected cardiovascular disease. These patients were more prone to demonstrate frequent ventricular premature complexes and had a higher incidence of multifocal ventricular premature beats and ventricular tachycardia. The ventricular premature complexes were also more likely to appear at lower heart rates during exercise in patients with cardiovascular disease. However, the appearance of unifocal ventricular premature complexes during maximal or near maximal exercise testing should not be equated with the presence of clinically significant cardiac disease.

Ventricular premature complexes appearing in an otherwise normal resting electrocardiogram have been said to be associated with an increased incidence of future coronary heart disease.[1,2] Similarly, the appearance of ventricular premature complexes during usual work activities has been associated with an increased incidence of subsequent coronary heart disease.[3] Reports on the significance of ventricular premature complexes in response to submaximal exercise testing have been conflicting.[4–6] The frequency and clinical significance of arrhythmias occurring in response to near maximal or maximal exercise has received little attention even though electrocardiographic testing under these conditions has become increasingly widespread.[7,8] The present study deals with the incidence and types of arrhythmias noted during maximal treadmill exercise testing in 650 men, all active members of the Indiana State Police Force.

Methods and Materials

Six hundred fifty male members of the Indiana State Police Force between 25 and 54 years of age underwent graded maximal treadmill exercise testing as part of a periodic physical evaluation program currently being conducted at the Indiana University Medical Center. Be-

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TABLE I

Staging Program For Graded Treadmill Exercise Testing

Stage	Time (min.)	Speed (miles/hour)	Grade (%)
I	3	2.0	3
II	3	3.3	6
III	3	3.3	9
IV	3	3.3	12
V	3	3.3	15
VI	3	3.3	18
VII	3	3.3	21

fore the exercise test each man gave a complete history and underwent a thorough physical examination. Routine laboratory studies included a complete blood count and urinalysis, determination of fasting blood sugar, blood urea nitrogen and uric acid and a serum lipid profile comprising triglyceride and cholesterol levels and a lipoprotein electrophoresis. A resting electrocardiogram and a posteroanterior and lateral roentgenogram of the chest were obtained for each man.

Our techniques for electrode application[9] and our staging program for graded exercise have been designed to obtain optimal noise reduction, thus permitting us to identify and interpret arrhythmias occurring during maximal exercise testing. Silver-silver chloride electrodes are placed in a modified bipolar V_5 position. The right-sided electrode is placed routinely in the RV_5 position, whereas the left-sided electrode is placed in the position that yields a QRS complex with a large R and small S wave. For any given patient this may range from the V_4 to V_6 position and either the fifth or sixth interspace. The desired placement of the left-sided electrode can be predetermined in the majority of patients by reviewing the 12 lead resting electrocardiogram. An indifferent or ground electrode is placed over the manubrium sternum. Our staging program for graded exercise is shown in Table I. The work load is increased by increments every 3 minutes until self-determined symptoms of exhaustion are indicated by the patient. The monitoring physician will terminate the test if the patient shows decreasing blood pressure, increasing pallor or a faltering of gait or if 3 or more consecutive ventricular premature complexes are observed.

The electrocardiogram is monitored continuously with an oscilloscope, and direct write-outs are recorded at selected intervals or whenever the monitoring physician observes an arrhythmia. The electrocardiographic signal is also recorded continuously on a magnetic tape along with an electronically generated time code. If a transient arrhythmia is observed during any period of the exercise test the data for that period are located by means of the time code, and a direct write-out is obtained. The data are again reviewed for arrhythmias after the exercise test during analog to digital conversion of the electrocardiographic signal in preparation for computer quantitation of the S–T segment response to exercise.[10]

Every recorded arrhythmia was studied to determine ventricular or supraventricular origin. The QRS configuration was used as the primary determinant of the origin of the arrhythmia, but the recordings were also studied for premature P wave activity and the presence of full compensatory pauses, with the possibility of aberrant intraventricular conduction of supraventricular impulses always in mind. Two consecutive premature beats were designated paired prematures; 3 or more consecutive prematures were considered tachycardia, either supraventricular or ventricular. Ventricular premature complexes were considered to be multifocal if 2 distinctly different premature QRS complexes with different coupling intervals appeared in the same stage of exercise at essentially the same heart rate. The stage of exercise during which an arrhythmia occurred was recorded as was the heart rate attained at that time. The frequency per minute of the premature complexes was also quantitated. If the frequency was 6 or less per minute the premature beats were considered "occasional"; if more than 6 were recorded per minute they were classified as "frequent."

The 650 subjects were divided into 3 age groups, 25 to 34, 35 to 44 and 45 to 54 years, to determine if there was an age-related difference in the incidence of arrhythmia during maximal exercise testing. The clinical and laboratory data for each subject were reviewed for evidence of cardiovascular disease. A diagnosis of arteriosclerotic heart disease was made if the patient gave a history typical for angina pectoris or if a previous myocardial infarction had been documented clinically. A diagnosis of hypertension was made if the patient demonstrated persistent systolic blood pressures greater than 160 mm Hg or diastolic blood pressures greater than 96 mm Hg during the medical evaluation. The subjects in each age group with definite or suspected cardiovascular disease were compared with those with no clinical evidence of cardiovascular disease for differences in the incidence of arrhythmias.

TABLE II

Incidence of Arrhythmias Observed During Maximal Treadmill Exercise Studies

Age Group (yr)	Patients Studied (no.)	Arrhythmia: Type	Occurrence: During Rest and Exercise	Occurrence: During Exercise Only
25–34	282	VPC	90 (32%)	81 (30%)
		SPC	15 (6%)	15 (6%)
		Both	3 (1%)	3 (1%)
35–44	283	VPC	108 (38%)	92 (33%)
		SPC	14 (5%)	14 (5%)
		Both	15 (5%)	15 (5%)*
45–54	85	VPC	40 (47%)	36 (42%)
		SPC	6 (7%)	6 (7%)
		Both	6 (7%)	6 (7%)†

* All supraventricular premature complexes during exercise only; 1 with ventricular premature complexes at rest and during exercise.

† All with supraventricular premature complexes during exercise only; 2 with ventricular premature complexes at rest only; 2 with ventricular premature complexes at rest and during exercise.

SPC = supraventricular premature complex; VPC = ventricular premature complexes.

Results

The number of subjects studied and the incidence of arrhythmias occurring during maximal exercise studies for each of the 3 age groups are shown in Table II. The incidence of both ventricular and supraventricular arrhythmias during exercise ranged from 37 percent in the 25 to 34 year age group to 56 percent in the 45 to 54 year age group. Ventricular premature complexes predominated in each age group with an incidence of 31 percent in the 25 to 34 year olds, 38 percent in the 35 to 44 year olds and 49 percent in the 45 to 54 year olds. The incidence of ventricular premature complexes increased significantly with increasing age ($P < 0.005$). A small number of patients in each age group were observed to have ventricular premature complexes at rest. The incidence was 2 percent in the 25 to 34 year, 5 percent in the 35 to 44 year and 10 percent in the 45 to 54 year age groups (Table II). Of the 34 subjects observed to have ventricular premature complexes on the resting electrocardiogram, (including those with both ventricular and supraventricular prematures) 21 (62 percent) continued to demonstrate ventricular prematures after the first stage of treadmill exercise. In 11 patients they were never totally suppressed with exercise; in 10 they were initially suppressed but then reappeared at near maximal or maximal exercise levels. The numbers of patients with ventricular premature complexes at rest in each age group were too small to make a valid comparison between normal subjects and those with suspected cardiovascular disease.

Supraventricular premature complexes were noted in 7 percent of the 25 to 34 year, 10 percent of the 35 to 44 year and 14 percent of the 45 to 54 year age groups (Table II). Although the incidence of supraventricular premature complexes appeared to increase with age, the differences between age groups were not statistically significant ($P < 0.05$). None of the 650 subjects had supraventricular premature complexes on the resting electrocardiogram.

TABLE III

Cardiovascular Abnormalities Detected in 650 Men Undergoing Maximal Treadmill Exercise Testing

Cardiovascular Abnormality	Age Group (no. of Patients)		
	25–34 (16)	35–44 (46)	45–54 (27)
Resting ECG abnormality	9	16	3
NSST–T wave changes	(5)	(8)	(2)
ALAD (—30° or more)	(3)	(7)	(1)
IVCD (QRS of 0.11 sec or more)	(1)	(1)	(0)
Positive exercise ECG*	2	8	9
Hypertension	4	8†	8†
Heart disease			
Arteriosclerotic	1	8	5
Valvular	0	6	2

* Horizontal S–T segment depression of 1 mm or more during or after exercise.

† Includes 1 subject with clinical hypertensive heart disease.

ALAD = abnormal left axis deviation; IVCD = intraventricular conduction defect; NSST–T wave changes = nonspecific S–T or T wave changes, or both.

Comparison of normal subjects and those with cardiovascular disease: Medical evaluation revealed definite or suspected cardiovascular disease in 89 of the 650 subjects (Table III). The incidence for each age group was 5 percent in the 25 to 34 year, 13 percent in the 35 to 44 year and 21 percent in the 45 to 54 year age groups. The incidence of ventricular premature complexes appearing during exercise in the normal subjects and the patients with definite or suspected cardiovascular disease is shown in Table IV, column 3. In each age group there was a greater incidence of ventricular premature complexes during exercise in the patients with evidence of cardiovascular disease as compared with the normal subjects; however, this increased incidence was statistically significant only in the 35 to 44 year age group ($P < 0.025$). The in-

TABLE IV

Incidence of Ventricular Arrythmias Observed During Maximal Treadmill Exercise Testing

Age Group (yr)	Patients Studied (no.)	All VPC	Frequency of VPC		Paired VPC	Multifocal VPC	Ventricular Tachycardia
			Occasional	Frequent			
25–34							
N	266	77 (29%)	55 (70%)	22 (30%)	6 (2.2%)	3 (1.1%)	1 (0.4%)
CVD	16	7 (44%)	3 (43%)	4 (57%)	0	0	0
35–44							
N	237	81 (34%)	55 (68%)	26 (32%)	11 (5.0%)	8 (3.4%)	4 (1.7%)
CVD	46	25 (54%)	13 (52%)	12 (48%)	6 (13.0%)	3 (6.5%)	2 (4.4%)
45–54							
N	58	25 (43%)	12 (48%)	13 (52%)	3 (5.0%)	1 (1.8%)	1 (1.8%)
CVD	27	13 (48%)	4 (31%)	9 (69%)	3 (11.0%)	3 (11.0%)	3 (11.0%)

CVD = patients with definite or suspected cardiovascular disease; N = normal subjects; VPC = ventricular premature complexes.

TABLE V

Incidence of Supraventricular Arrythmias Observed During Maximal Treadmill Exercise Testing

Age Group (yr)	Patients Studied (no.)	Supraventricular Premature Complexes	Supraventricular Tachycardia
25–34			
N	266	17 (6.0%)	2 (0.8%)
CVD	16	1 (6.0%)	0
35–44			
N	237	25 (11.0%)	0
CVD	46	3 (6.5%)	1 (2.2%)
45–54			
N	58	8 (14.0%)	1 (1.8%)
CVD	27	4 (15.0%)	0

Abbreviations as in Table IV.

cidence of supraventricular complexes in men with and without cardiovascular disease is shown in Table V. There was no significant increase in the incidence of supraventricular premature complexes in the patients with cardiovascular disease as compared to the normal men. Paroxysmal supraventricular tachycardia was observed only rarely in each age group.

The frequency of all ventricular premature complexes observed in the subjects with and without evidence of cardiovascular disease is listed in Table IV, columns 4 and 5. The incidence of frequent ventricular premature complexes in the normal subjects was 30 percent in the 25 to 34 year, 32 percent in the 35 to 44 year and 52 percent in the 45 to 54 year age groups. The incidence of frequent ventricular premature complexes in the patients with cardiovascular disease was greater than that in the normal subjects in each age group.

The incidence of ventricular arrhythmias other than isolated, unifocal premature complexes is listed for each age group in Table IV, columns 6 to 8. A small number of normal patients in each age group demonstrated paired or multifocal ventricular premature complexes or ventricular tachycardia. The incidence of each type of arrhythmia was greater in the patients with definite or suspected cardiovascular disease except in the 25 to 34 year olds of whom only a small number had evidence of cardiovascular disease.

TABLE VI

Heart Rate at Time of Appearance of Ventricular Premature Complexes During Exercise Testing

Age Group (Yr)	Heart Rate	
	<150/Min	≥150/Min
25–39		
N	28 (24%)	88 (76%)
CVD	15 (70%)	7 (30%)
40–54		
N	17 (25%)	50 (75%)
CVD	14 (60%)	9 (40%)

Abbreviations as in Table IV.

In the men without evidence of cardiovascular disease the heart rate at the time of appearance of ventricular arrhythmias was 150 beats/min or more in 76 percent of the cases (Table VI). This finding held true regardless of the patient's age. In the patients with cardiovascular disease, ventricular premature complexes were much more likely to appear at heart rates below 150 beats/min (Table VI). This difference in exercise heart rates at the time of appearance of ventricular premature complexes in normal men and patients with cardiovascular disease was highly significant ($P < 0.001$). Supraventricular prematures occurred at heart rates over 150 beats/min in more than 90 percent of the patients in whom they were observed regardless of the clinical diagnosis.

Discussion

The present study demonstrates that arrhythmias, usually transient and in the form of unifocal ventricular or supraventricular premature complexes, are quite common during strenuous exercise testing in men without clinical evidence of heart disease. The arrhythmias are usually observed at a heart rate of 150 beats/min or greater, and they occur most commonly during the last minute of maximal exercise or during the first 30 seconds of recovery (Fig. 1 and 2). Conversely, in patients with clinical evidence of cardiovascular disease, ventricular premature complexes are more likely to appear at exercise heart rates below 150 beats/min (Table VI). Patients with evidence of cardiovascular disease are more prone to demonstrate frequent or multifocal ventricular premature complexes or ventricular tachycardia (Table IV), but identical arrhythmias were observed in patients without cardiovascular disease in all age groups studied (Fig. 1 and 2). The incidence of ventricular premature complexes increased with age in the normal patients and those with clinical evidence of cardiovascular disease (Table IV). For any given age group, the incidence of ventricular premature complexes was greater in the patients with evidence of cardiovascular disease. The incidence of supraventricular premature complexes also increased with age but did not appear to be greater in patients with cardiovascular disease (Table V).

Differentiation between premature complexes of ventricular and supraventricular origin can be difficult during the rapid heart rates of maximal or near maximal exercise. We were rarely able to identify premature P waves preceding the premature QRS complexes with a normal or supraventricular configuration. Furthermore, the majority of premature complexes with a normal QRS con-

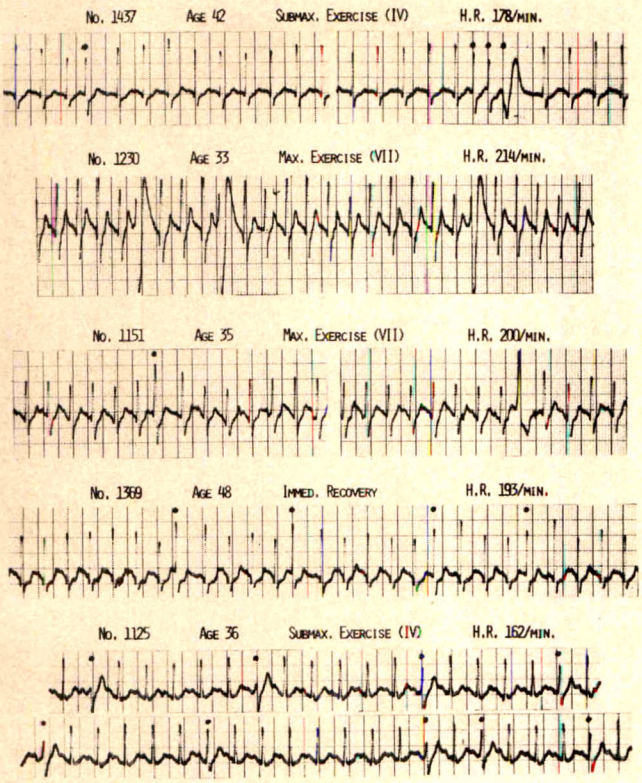

Figure 1

Figure 1. Patient 1437. The electrocardiographic recording to the left demonstrates an isolated premature QRS complex with a supraventricular configuration. There is no identifiable P wave preceding the premature QRS complex, and it is encompassed by a full compensatory pause suggesting that the ectopic impulse arose within the atrioventricular node or the bundle of His. The recording to the right demonstrates 3 consecutive supraventricular premature QRS complexes. The last of these complexes is conducted aberrantly when the R–R interval exceeds a rate of 300 beats/min. An alternative explanation is that the last premature QRS complex represents a ventricular premature complex.

Patient 1230. Frequent unifocal ventricular premature complexes observed during maximal exercise in a 33 year old man with no clinical evidence of heart disease.

Patient 1151. The electrocardiographic recording to the left demonstrates an isolated premature QRS complex with a supraventricular configuration. The premature complex is not preceded by an identifiable P wave and it is encompassed by a complete compensatory pause suggesting that the ectopic impulse arose within the atrioventricular node or the bundle of His. The recording to the right demonstrates another premature QRS complex recorded during the same stage of exercise. This complex has a left bundle branch block type QRS configuration suggesting that it is ventricular in origin but it is not encompassed by a full compensatory cause. This premature complex may be the result of an ectopic supraventricular impulse conducted aberrantly within the ventricles due to the short coupling interval to the preceding normal sinus QRS complex.

Patient 1369. Frequent premature QRS complexes of supraventricular configuration occurring during the immediate recovery period of a maximal exercise test. The coupling intervals of the premature complexes to the preceding normal sinus QRS complexes are variable but each premature complex is encompassed by a complete compensatory pause and there are no identifiable P waves preceding the premature beats. This places the origin of the ectopic impulses in or below the atrioventricular node.

Patient 1125. Frequent ventricular premature QRS complexes recorded during submaximal exercise in a clinically normal 36 year old man. There is a marked variability of the coupling intervals between the premature complexes and the preceding normal sinus complexes and there are frequent fusion beats. This arrhythmia represents a ventricular parasystole with a parasystolic rate of 83 beats/min (interectopic interval of 0.72 second, third and fourth premature complexes, bottom recording).

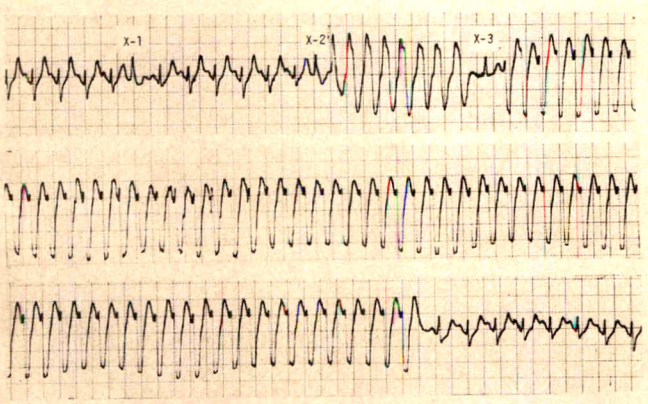

Figure 2

Figure 2. Patient 1113. Rapid ectopic tachycardias with aberrant QRS complexes occurring in the immediate post-exercise period in a clinically normal 36 year old man. The first group of consecutive premature QRS complexes (**top recording**) is initiated by a slightly aberrant premature complex designated X-2. The following 2 QRS complexes then demonstrate a progressively greater degree of aberrancy. An isolated premature QRS complex (X-1) is also present in the top recording; it is identical to X-2 and is not encompassed by a full compensatory pause. These findings support a supraventricular (atrial) origin for these arrhythmias. The first group of rapid aberrant QRS complexes terminates spontaneously and is followed after a short pause by a QRS complex designated X-3 which is quite similar to X-1 and X-2. This complex is then followed by a series of rapid aberrant premature QRS complexes with a polarity opposite that of the first series of rapid ectopic beats. Both runs of rapid tachycardia are slightly irregular, but the rates per minute are nearly comparable. The second longer series of consecutive ectopic complexes may be of ventricular origin, but aberrancy of supraventricular impulses due to a different intraventricular conduction defect cannot be ruled out.

figuration were found to be associated with a complete compensatory pause suggesting an origin in or below the atrioventricular node (Fig. 1). This finding leaves open the possibility that some of the premature contractions which we classified as ventricular in origin because of their aberrant configuration may have been supraventricular complexes with aberrant intraventricular conduction (Fig. 1 and 2).

Clinical implications: The clinical significance of ventricular premature complexes occurring in response to strenuous exercise testing remains to be determined. The incidence of multifocal ventricular premature complexes and ventricular tachycardia was quite low in the normal men in each age group studied, and the appearance of these arrhythmias during exercise testing should be viewed as suspect of underlying cardiac disease. However, the diagnosis of multifocal ventricular premature complexes should be made with caution during graded exercise testing. The usual criteria of different QRS configurations with different coupling intervals to the preceding normal sinus QRS are not valid during the stepwise increments in heart rate of graded exercise. The coupling interval of unifocal ventricular premature complexes tends to decrease as the exercise heart rate increases, and a gradual change in the QRS configuration with each increment in heart rate is commonly observed. The configuration of unifocal ventricular premature complexes during maximal or near maximal exercise may be grossly different from that of premature complexes from the same focus during the early stages of exercise at relatively slow heart rates. For these reasons we make the diagnosis of multifocal ventricular premature complexes only when there is a distinct change in the configuration of the premature complexes at a time when the heart rate is nearly constant. Our projected long term follow-up of these patients through periodic medical evaluations and maximal exercise testing will determine the prognostic significance of the arrhythmias observed during strenuous exercise testing. The fact that the unifocal ventricular premature complexes are much more common at heart rates above 150 beats/min can be interpreted as indicative of subclinical cardiac disease which is "unmasked" by strenuous exercise testing. However, we believe that changes in the electrophysiologic properties of conduction favoring reentry or an increase in sympathetic tone favoring an increase in automaticity are more reasonable explanations for the frequent ventricular premature complexes observed during maximal exercise testing and, thus, these premature beats do not necessarily indicate a pathologic state.

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The QRS Loop in Left Anterior and Posterior Hemiblocks

Vectorcardiographic Study During Selective Coronary Arteriography

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The vectorcardiographic characteristics of transient left intraventricular hemiblocks seen during selective coronary arteriography were studied in 26 patients. QRS duration was slightly but significantly increased. In left anterior hemiblock the frontal plane QRS loop rotated leftward and typically became largely open in this plane, encircling a wide area with a counterclockwise inscription of the QRS loop, and the maximal and terminal QRS vectors rotated leftward and were posteriorly directed. In left posterior hemiblock the frontal plane QRS loop rotated rightward and typically became largely open in this plane, encircling a wide area with a clockwise inscription of the QRS loop; the maximal QRS vector rotated rightward and was anteriorly deviated, whereas the terminal QRS vector rotated toward the right posteroinferior quadrant. In both cases, the initial QRS vector was not significantly modified. The changes observed in cases with a control QRS axis ranging from −10 to −90° suggest that these tracings usually correspond to incomplete forms of left anterior hemiblock; the orientation of terminal QRS vectors toward the right posterosuperior quadrant in cases of left anterior hemiblock corresponds to the addition of delayed activation of the posterior wall of the left ventricle. The changes observed in cases of "periinfarction block" suggest that these tracings result from the association of initial QRS anomalies typical of myocardial infarction with abnormally directed terminal vectors of a type characteristic of left anterior or posterior hemiblock. QRS axis deviation observed in cases of right or left bundle branch block may result from an associated left anterior or posterior hemiblock.

QRS modifications induced in man by selective coronary arteriography can be considered transient left anterior or posterior hemiblock.[1–4] Although the resulting QRS changes in standard leads I, II and III have been analyzed,[1–6] there are few publications concerning modifications of the precordials leads[2,6] and of the frontal and horizontal vectorcardiograms.[7] The aim of this work was to study the QRS loop changes observed during selective coronary arteriography in order to assess the vectorcardiographic patterns of the left intraventricular hemiblocks thus obtained.

Material and Methods

Twenty-six consecutive patients referred for selective coronary arteriography were studied. During selective injection of contrast material (Vasurix 38, Laboratoire Guerbet, Saint-Ouen, France) into the coronary arteries, frontal and horizontal vectorcardiograms were successively obtained. A modified Frank[8] lead system (1507A Vector Programmer, Hewlett Packard) was utilized in which the horizontal plane

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TABLE I

Data (mean ± SE) from Tracings Obtained Before and After Left Anterior and Left Posterior Hemiblocks Induced by Selective Coronary Arteriography

	Group I (13 Patients)			Group II (6 Patients)			Group III (5 Patients)		
	Control	LAH	LPH	Control	LAH	LPH	Control	LAH	LPH
QRS duration	7.9 ± 1.3	8.9 ± 1.3‡	8.4 ± 1.2†	8.2 ± 0.3	9 ± 0.8	8.6 ± 0.6	7.8 ± 1	9.6 ± 1.9	8.6 ± 1.6*
Frontal VCG									
CW	9	1	10	...	...	2	2	3	5
CCW	3	7	...	5	5	3	2	2	...
"8"	1	5	...	1	...	1	1	...	...
ÂVi	−156 ± 55	−156 ± 59	−167 ± 50	+128 ± 55	+102 ± 42	+100 ± 43	−113 ± 70	−123 ± 63	−113 ± 67
tVi	0.9 ± 0.4	1 ± 0.4	1 ± 0.3	0.7 ± 0.4	0.5 ± 0.2	0.7 ± 0.4	1.1 ± 0.7	1.3 ± 0.6§	1.3 ± 0.7
ÂVm	+40 ± 14	+20 ± 14‡	+54 ± 15§	+11 ± 18	+11 ± 17	+49 ± 32*	+57 ± 17	+52 ± 7	+65 ± 18
tVm	3.7 ± 0.6	4.1 ± 0.7†	3.9 ± 0.5	3.5 ± 0.6	3.7 ± 0.9	3.9 ± 0.6	3.9 ± 0.9	4.6 ± 1.1*	3.9 ± 0.8
Âvt	(0 − 360)	−54 ± 45	+148 ± 46	−93 ± 33	−84 ± 15*	−135 ± 24*	+165 ± 91	−70 ± 83	+137 ± 56
Horizontal VCG									
CW	...	...	1	...	...	...	...	...	...
CCW	13	13	8	6	5	5	5	5	5
"8"	...	...	1	...	...	1	...	...	...
ÂVi	+130 ± 18	+136 ± 26	+138 ± 28	+67 ± 65	+52 ± 68	+65 ± 61	+130 ± 90	+130 ± 88	+127 ± 85
ÂVm	+6 ± 18	+6 ± 23	+15 ± 19*	−9 ± 25	−6 ± 28	+3 ± 31	−34 ± 28	−26 ± 23	−25 ± 22
VVm	1.7 ± 0.7	2.3 ± 0.9‡	1.7 ± 0.6	1.1 ± 0.7	1.6 ± 0.7§	1.1 ± 0.5	1.6 ± 0.7	2.1 ± 0.7§	1.4 ± 0.7
ÂVt	−108 ± 36	−67 ± 27†	−131 ± 33*	−101 ± 31	−86 ± 27	−108 ± 56	−102 ± 50	−80 ± 54	−92 ± 43
VVt	0.8 ± 0.6	1 ± 0.7	0.9 ± 0.3§	0.8 ± 0.5	1 ± 0.8	0.8 ± 0.4	...	...	...

* P <0.05; † P <0.01; ‡ P <0.001; § P <0.02.

Â, t and V = orientation, timing (in hundredths of a second) and voltage (in mv), respectively, of the initial (Vi), maximal (Vm) and terminal (Vt) QRS vectors; CCW, CW and "8" = counterclockwise, clockwise and figure-of-eight inscription of QRS loop; LAH = left anterior hemiblock; LPH = left posterior hemiblock; VCG = vectorcardiogram.

electrodes were placed in the sixth intercostal space, in order to avoid projection of the radiopaque electrodes on the coronary cineangiograms. The QRS loop was continuously displayed on an oscilloscope (Sanborn 780-6A Visoscope), and the loop that appeared to be most modified was photographed with a Polaroid camera.

Orientation, configuration and rotation of QRS loop in the frontal and horizontal planes were studied in control vectorcardiograms and in those obtained during selective coronary arteriography. The duration of the QRS loop and the timing, orientation and voltage of the initial, maximal and terminal QRS vectors were also measured in both conditions. Statistical analysis was performed in each group by the use of Student's paired *t* test, taking into account for each patient the variation from the control data.

Patients were divided into 4 groups (Table I) according to findings in the control tracings. Group I included 13 patients, 9 male and 4 female, with normal ventricular depolarization. The patients ranged in age from 32 to 60 years; in 8, coronary cineangiograms revealed normal coronary arteries, in 4, isolated stenosis of a single coronary artery, and in 1, stenosis of several coronary arteries. Group II included 6 patients, 5 male and 1 female, with a frontal plane QRS axis between −10 and −90°. The patients ranged in age from 41 to 63 years; in 2, coronary arteriograms revealed normal coronary arteries, and in 4, severe and diffuse coronary artery stenosis. Group III included 5 patients, 4 male and 1 female, with old myocardial infarction or right coronary artery occlusion with left to right coronary artery anastomoses, or both. The patients [illegible] age from 48 to 61 years; in all 5 coronary [illegible] grams revealed severe and diffuse coron[illegible] stenosis. Group IV comprised 2 men, 18 an[illegible] old, with idiopathic cardiomyopathy. In 1, co[illegible] trocardiograms showed intermittent complete[illegible] dle branch block, and in the other, a combined[illegible] of right ventricular hypertrophy and incomple[illegible] bundle branch block; in both men, coronary [illegible] grams showed normal findings.

Results

Group I (Table I): This group comprised [illegible] tients with normal ventricular depolarization[illegible] a frontal QRS axis ranging from +10 to +7[illegible] the control electrocardiograms.

Left coronary artery opacification (Table I, Fi[illegible] 1 to 3) increased QRS duration by 0.01 second ($P < 0.001$). The QRS loop deviated toward the left posterosuperior quadrant and became largely open in the frontal plane, usually encircling a wide area with an isolated or predominant counterclockwise inscription of the QRS loop. In the frontal plane, the initial QRS vector was not significantly modified, this vector pointing in 7 cases toward the right superior quadrant (Fig. 1); the maximal QRS vector rotated toward the left superior quadrant ($P < 0.001$), and its timing was delayed ($P < 0.01$); the terminal vector deviated to the left and superiorly. In the horizontal plane, the initial

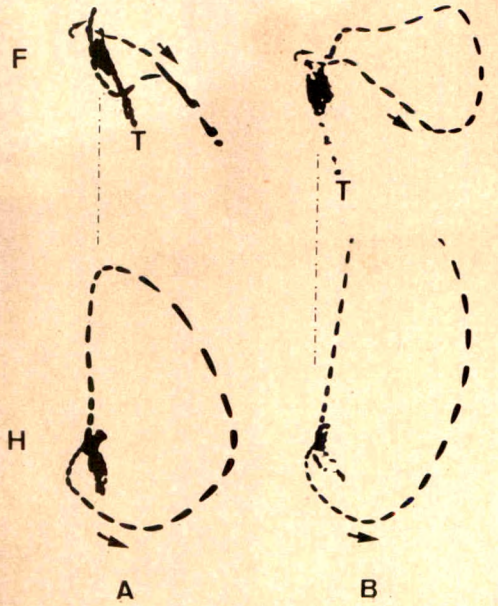

Figure 1. Left anterior hemiblock observed during selective left coronary arteriography. **A,** control tracing; **B,** left anterior hemiblock. F and H = frontal and horizontal vectorcardiograms, respectively. Time intervals, 4 dots every 0.01 second. Note the absence of significant change of the initial Q vectors.

QRS vector was not significantly modified; the maximal QRS vector rotated toward the left posterior quadrant (not significant), and its voltage increased significantly ($P < 0.001$); the terminal QRS vector deviated to the left and posteriorly ($P < 0.01$).

Right coronary artery opacification (Table I, Fig. 3 and 4) resulted in an increased QRS duration by 0.005 second ($P < 0.01$). In the frontal plane the QRS loop deviated to the right and inferiorly and became largely open in this plane, usually encircling a wide area with an isolated or predominant clockwise inscription of the QRS loop. In the horizontal plane the QRS loop inscription remained counterclockwise in all but 2 cases. In the latter the QRS loop showed a figure-of-eight pattern with clockwise rotation of the anteriorly directed terminal vectors (incomplete right bundle branch block pattern). In the frontal plane, the initial QRS vector was not significantly modified, and in 5 cases pointed toward the right inferior quadrant (Fig. 3); the maximal QRS vector deviated to the right ($P < 0.02$), and the terminal vector rotated toward the right inferior quadrant. In the horizontal plane, the initial QRS vector was not significantly modified; the maximal QRS vector deviated anteriorly ($P < 0.05$), whereas the terminal vector rotated toward the right posterior quadrant ($P < 0.05$) and its voltage was significantly increased ($P < 0.02$).

Group II (Table I): In this group were 6 patients with a frontal plane QRS axis of −10 to −90° on the control electrocardiogram.

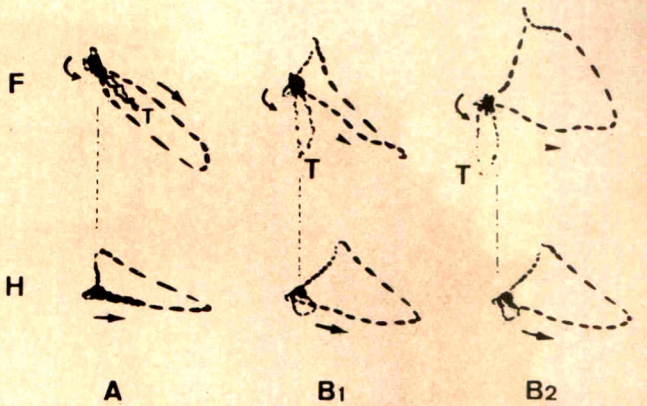

Figure 2. Left anterior hemiblock observed during left coronary arteriography. **A,** control tracing; **B1** and **B2,** 2 successive stages of left anterior hemiblock.

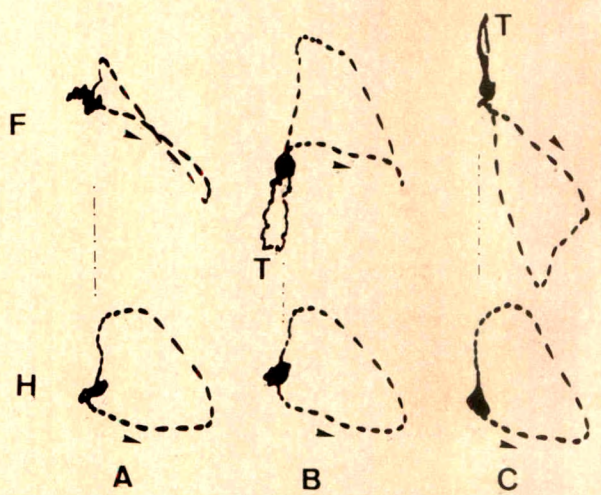

Figure 3. Left anterior and posterior hemiblocks obtained during selective coronary arteriography. **A,** control tracing; **B,** left anterior hemiblock; **C,** left posterior hemiblock. Note the absence of significant change of the initial Q vectors.

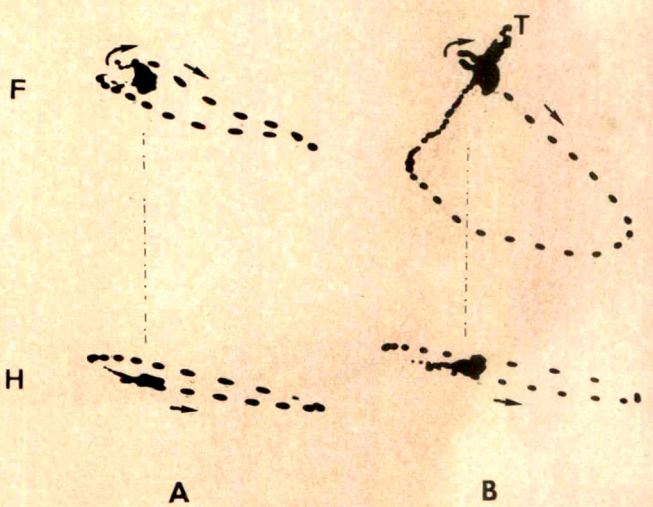

Figure 4. Left posterior hemiblock obtained during right coronary arteriography. **A,** control tracing; **B,** left posterior hemiblock.

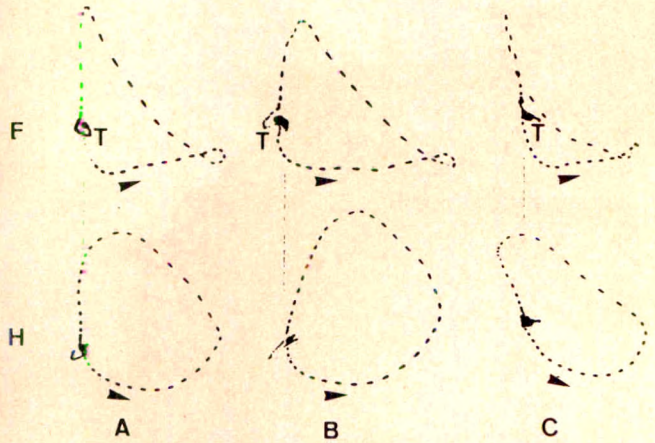

Figure 5. Left intraventricular hemiblocks observed in a case with a control QRS axis pointing to −25° (**A**). **B**, QRS loop changes observed during left coronary arteriography. **C**, QRS loop changes observed during right coronary arteriography.

Left coronary arteriography (Table I, Fig. 5) resulted only in significant deviation of the terminal QRS vectors toward the left superior quadrant ($P < 0.05$) and in increased voltage of the maximal horizontal QRS vectors ($P < 0.02$).

Right coronary arteriography (Table I, Fig. 5) resulted in clockwise inscription of the frontal QRS loop in 2 cases. In the horizontal plane, the QRS loop inscription remained counterclockwise in all but 1 case, in which it showed a figure-of-eight pattern with clockwise rotation of the anteriorly deviated terminal vectors (incomplete right bundle branch block pattern). In the frontal plane the maximal QRS vector deviated to the right ($P < 0.05$), whereas the terminal vector rotated toward the right superior quadrant ($P < 0.05$).

Group III (Table I): This group comprised 5 patients with an old myocardial infarction or left to right coronary artery anastomoses, or both; the coronary arteriograms revealed severe and diffuse coronary artery stenoses in all cases.

Left coronary artery opacification (Table I) resulted in an insignificant increase of the QRS duration. The frontal plane QRS loop deviated slightly toward the right and became largely open with an isolated clockwise rotation in the 3 patients with left to right coronary artery anastomoses. In the other 2 patients, it deviated slightly toward the left and showed predominant counterclockwise inscription. The rightward deviation and the clockwise inscription of the QRS loop probably represent the late phase of the biphasic reaction which usually occurs in patients with left to right coronary artery anastomoses. The timing of the initial and maximal QRS vectors and the voltage of the maximal horizontal QRS vector were significantly increased.

Right coronary artery opacification (Table I) resulted in a significant increase of the QRS duration ($P < 0.05$). The frontal QRS loop became in all cases largely open and was inscribed clockwise, whereas the initial, maximal and terminal QRS vectors were not significantly modified.

Group IV: The 2 patients in this group had an electrocardiographic pattern of right or left bundle branch block. One of these patients had intermittent complete left bundle branch block (Fig. 6), which resulted in a shift of the QRS axis from +60 (normal conduction) to +5° (complete left bundle branch block). In this case left coronary artery opacification (Fig. 6) was accompanied by an increase of the QRS duration from 0.13 to 0.15 second; the frontal plane QRS loop deviated to the

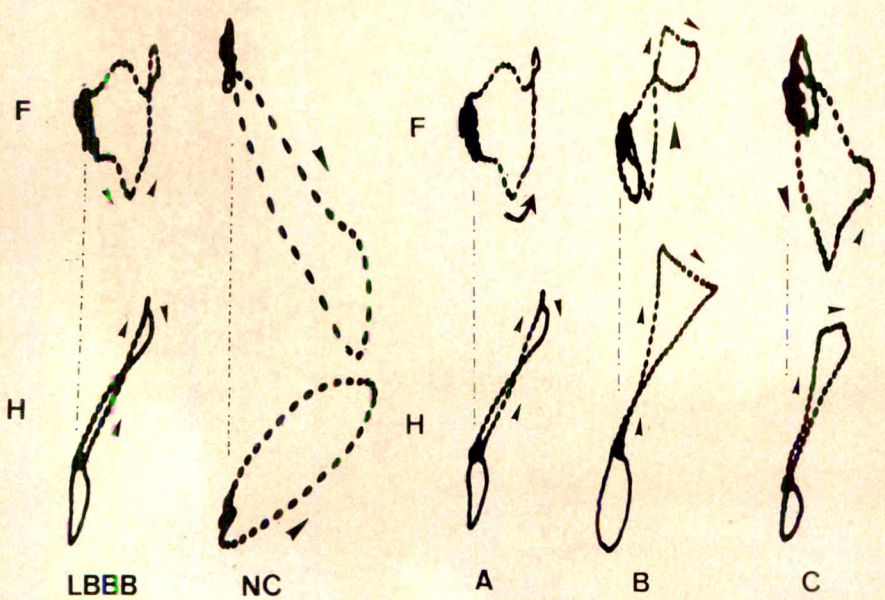

Figure 6. QRS loop changes in intermittent complete left bundle branch block (LBBB). **A**, control tracing before selective coronary arteriography. **B** and **C**, QRS loops obtained during selective left and right coronary artery opacification, respectively. NC = normal conduction.

left and showed a figure-of-eight configuration; the QRS axis rotated from +5 to −20°. Right coronary artery opacification (Fig. 6 and 7) increased the P–R interval from 0.19 to 0.21 second and the QRS duration from 0.13 to 0.14 second; the frontal plane QRS loop was deviated to the right, but the inscription remained counterclockwise; the QRS axis changed from +5 to +75°.

The second patient had a pattern of combined right ventricular hypertrophy and incomplete right bundle branch block. Left coronary artery opacification (Fig. 8) resulted in mild superior deviation of the frontal QRS loop figure-of-eight pattern and in mild leftward rotation of the maximal QRS vector, the terminal vectors pointing to ±180° in both the frontal and horizontal planes. Right coronary artery opacification (Fig. 8) resulted in rightward deviation of the frontal QRS loop, which became largely open in this plane, encircling a wide area with a clockwise inscription of the QRS loop; the maximal QRS vector rotated rightward and increased in magnitude, and the terminal vector changed from +120 to +100°.

Discussion

The vectorcardiographic characteristics of left intraventricular hemiblocks were tentatively studied in patients who had either electrocardiograms meeting the accepted criteria for the diagnosis of left hemiblock[9,10] or aberrant QRS loops resulting from atrial pacing.[11] These methods do not make it possible to rule out the presence of combined intraventricular conduction disturbance, namely, incomplete left bundle branch block.

Selective coronary arteriography provides an opportunity to study the vectorcardiographic changes related to left intraventricular hemiblocks under nearly experimental conditions.[1-3] This study showed that left anterior hemiblock, resulting from selective opacification of the left coronary artery, was accompanied by a significant but slight increase of the QRS duration; the frontal QRS loop deviated to the left and became largely open in this plane, encircling a wide area with counterclockwise inscription; and the maximal and terminal QRS vectors rotated toward the left posterosuperior quadrant. Left posterior hemiblock, resulting from selective opacification of the right coronary artery, was accompanied by a significant but slight increase of the QRS duration; the frontal plane QRS loop deviated to the right and became largely open in this plane encircling a wide area with a clockwise inscription; the maximal QRS vector deviated to the right and anteriorly, whereas the terminal vector rotated toward the right posteroinferior quadrant.

In both left anterior and posterior hemiblocks the initial QRS vector was not significantly modified; thus, this vector was rightward and superiorly directed in some cases of left anterior hemiblock (Fig. 1) and rightward and inferiorly directed in some cases of left posterior hemiblock (Fig. 3). This finding is in disagreement with the conclusions of Rosenbaum et al.,[12] who specifically described the initial "qI-rII-rIII" and "rI-qII-qIII" patterns as a characteristic diagnostic feature of left anterior and posterior hemiblocks, respectively. This discrepancy may be explained if one assumes that left intraventricular hemiblocks observed during selective coronary arteri-

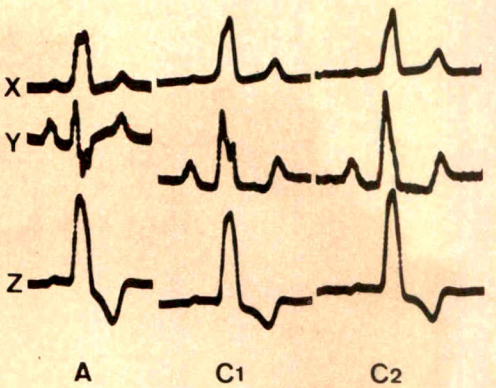

Figure 7. Orthogonal leads (X, Y and Z) in intermittent complete left bundle branch block (same case as in Figure 6). **A,** control tracing. **C1** and **C2,** 2 successive stages of combined left bundle branch block and left posterior hemiblock obtained during right coronary arteriography. Note the modification of the lead Y contour. Sweep speed = 50 mm/sec.

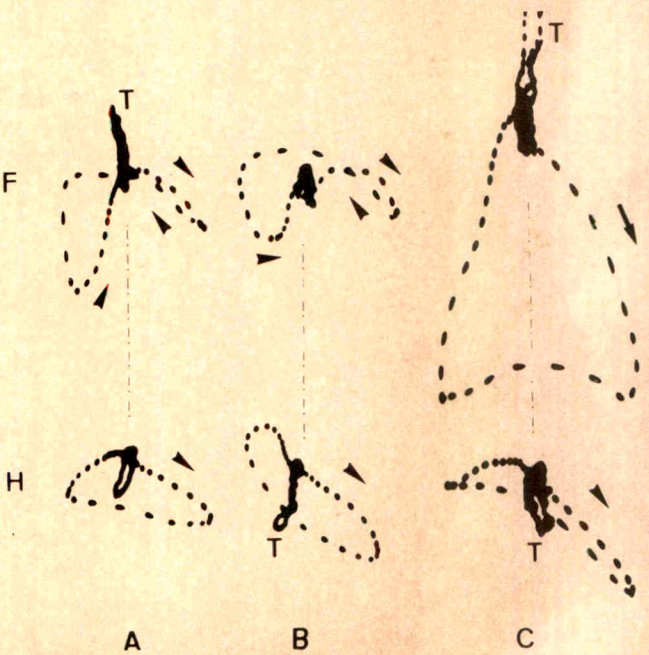

Figure 8. QRS loop changes in combined right ventricular hypertrophy and incomplete right bundle branch block. During left coronary arteriography (**B**) the figure-of-eight pattern of the frontal QRS loop (F) showed slight superior deviation. During right coronary arteriography (**C**) the frontal QRS loop (F) deviated to the right and became largely open, encircling a wide area with a clockwise inscription corresponding to the association of left posterior hemiblock with incomplete right bundle branch block. **A** = control tracing.

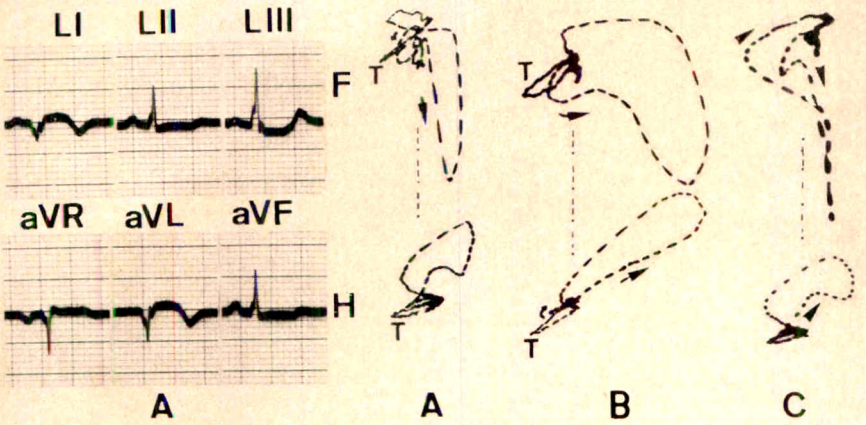

Figure 9. QRS loop modifications observed in a patient with initial QRS deformity of anterolateral myocardial infarction (initial QI-RIII pattern) and terminal QRS deformity of left posterior hemiblock (terminal SI-RIII pattern). In the control tracings (**A**) the mean initial and last 0.04 second QRS vectors are directed inferiorly and to the right. Left coronary arteriography (**B**) resulted in widening of the angle formed by these 2 vectors, whereas right coronary arteriography (**C**) resulted in a rightward deviation of both vectors, which then pointed again in the same direction.

ography are indeed parietal hemiblocks resulting from the direct action of the radiopaque substance on nonspecific myocardial fibers.[1-3] Incomplete right bundle branch block occurring in 2 patients during selective right coronary arteriography provides further evidence for this possibility. This pattern probably resulted from the delayed activation of the right ventricular myocardium, directly induced by the radiopaque substance.

Similar but less important vectorcardiographic changes were observed during selective left and right coronary artery opacification in patients with a control QRS axis of −10 to −90°. This fact suggests that these initial tracings usually correspond to incomplete forms of left anterior hemiblock. Whereas selective left coronary arteriography deviated the maximal and terminal QRS vectors toward the left posterosuperior quadrant (Fig. 5), selective right coronary arteriography resulted in an anterior and rightward deviation of the maximal QRS vector. This vector then pointed toward the left anterior inferior quadrant, whereas the terminal vector rotated toward the right posterosuperior quadrant (Fig. 5). Thus, the QRS loop in these cases showed the type II pattern described by Testoni[9]; apparently these peculiar tracings correspond to the association of left anterior hemiblock with delayed activation of the posterior wall of the left ventricle.[9]

Relation to peri-infarction block: The vectorcardiographic changes observed in patients with an old myocardial infarction provide the opportunity to study the relation between left intraventricular hemiblocks and "peri-infarction block.[13,14] The basic feature of this peculiar QRS deformity is, according to Grant,[15-17] "the association of abnormally directed initial QRS forces of a type characteristic of antero-lateral or diaphragmatic myocardial infarction with abnormally directed terminal QRS forces pointing in a direction opposite to initial vectors." That the abnormal orientation of the terminal QRS vectors is due to a left anterior or posterior hemiblock is proved by selective coronary arteriography.[13] Indeed, in these cases selective coronary arteriography resulted in little or no change of the mean first 0.04 second QRS vector, whereas the mean last 0.04 second QRS vector is modified according to the type of peri-infarction block. Therefore, in the case of diaphragmatic peri-infarction block, the mean last 0.04 second QRS vector remained unmodified during right coronary arteriography and rotated leftward during left coronary arteriography; thus, the characteristic wide opposition of the mean first and last 0.04 second QRS vectors of diaphragmatic peri-infarction block remained unmodified during left posterior hemiblock and disappeared during left anterior hemiblock. Similarly, in the case of anterolateral peri-infarction block the orientation of the mean last 0.04 second QRS vector remained unmodified during left coronary arteriography, whereas this vector rotated rightward during right coronary arteriography; thus, the characteristic wide opposition of the initial and terminal QRS vectors of anterolateral peri-infarction block remained unmodified during left anterior hemiblock and disappeared during left posterior hemiblock.[13]

A second aspect of the postmyocardial infarction QRS deformity which is well explained by selective coronary arteriography is illustrated in Figure 9. The abnormally directed initial vector is characteristic of anterolateral myocardial infarction, whereas the direction of the terminal vector is that of left posterior hemiblock.[17] Indeed, this peculiar pattern remained unmodified during left posterior hemiblock induced by right coronary artery opacification and disappeared during the left anterior hemiblock induced by left coronary arteriography.

Relation to axis deviation: Left and right QRS axis deviations observed in cases of left or right bundle branch block are now generally attributed to associated left anterior or posterior hemiblock.[12] Indeed, in the case of complete left bundle branch block, selective left coronary arteriography, which usually induced left anterior hemiblock, resulted in a mild leftward QRS deviation, whereas selective right coronary arteriography, which usually in-

duced left posterior hemiblock, rotated the QRS loop to the right. These findings indicate that left intraventricular hemiblocks may result in a frontal QRS axis deviation in spite of the presence of complete left bundle branch block, although the inscription of the horizontal QRS loop remained clockwise in both cases. The association of right bundle branch block with right or left axis deviation is now usually considered an expression of bilateral bundle branch block.[12,18,19] Selective coronary arteriography provides new evidence for this fact.[13] This was shown in the case of right bundle branch block, in which left anterior hemiblock induced by left coronary artery opacification resulted in a mild superior deviation of the frontal QRS loop, whereas left posterior hemiblock induced by right coronary artery opacification resulted in rightward deviation of the frontal QRS loop. This loop became largely open in this plane encircling a wide area with a clockwise inscription.

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The Incidence and Mortality of Intraventricular Conduction Defects in Acute Myocardial Infarction

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The incidence of intraventricular conduction defects during sinus mechanism was 24 percent in 212 consecutive cases of acute myocardial infarction observed in a coronary care unit. Patients with intraventricular conduction defects had a higher mean age than that for the entire series ($P < 0.01$), and death occurred at a younger age than in patients without such defects ($P < 0.1$). The most common isolated defect was left anterior hemiblock (incidence of 9.4 percent). The next most common conduction defect was incomplete bilateral bundle branch block (incidence 7.5 percent); more than half of these patients had right bundle branch block with left anterior hemiblock. Far less frequent were isolated complete right bundle branch block and complete left bundle branch block. Left posterior hemiblock was rare and was not seen in patients without other intraventricular conduction defects either transient or permanent. The hospital mortality rate of the entire series was 21.2 percent. The mortality rate among patients with intraventricular conduction defects was 47 percent which is significantly different from that for the entire series ($P < 0.01$) and from a series matched by sex and age ($P < 0.01$). The most innocuous intraventricular conduction defect was left anterior hemiblock (in-hospital mortality rate 25 percent). This was statistically not different from the mortality rate in the total series. Higher mortality rates were associated with other conduction defects which produced QRS prolongation and bifascicular block.

Electrocardiographic criteria for the diagnosis of intraventricular conduction defects have been clarified in recent years by experimental studies[1] and by correlation of pathologic and electrocardiographic findings.[1–7] As a consequence, data defining the incidence and prognosis of intraventricular conduction defects in acute myocardial infarction are accumulating rapidly.[8–12] However, most studies provide information on selected conduction disturbances, and emphasis has frequently been on the development of complete atrioventricular (A–V) block.[13–14] No large series has dealt with the incidence and comparative mortality rates of specific intraventricular conduction defects in acute myocardial infarction in the presence of sinus mechanism. Perhaps differences in mortality rate may best be judged in a single series in which patterns of management apply equally to patients with the several kinds of conduction disturbances. In this communication a spectrum of intraventricular conduction defects in acute myocardial infarction is analyzed, with emphasis on the effect on in-hospital mortality rates.

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Clinical Material and Criteria for Diagnosis

A total of 208 patients with 212 consecutive attacks of acute transmural myocardial infarction were treated in a 10 bed coronary care unit[15] at Good Samaritan Hospital in Dayton, Ohio, in 1967 and 1968. In the great majority of patients admission to the hospital took place within the first 24 hours after onset of the acute episode.

The diagnosis of myocardial infarction in this series was documented in each case by a suggestive history of chest pain correlated with the appearance of diagnostic Q waves and appropriate elevation of enzyme levels. When left bundle branch block was present before the acute episode, substantial increase of enzymes in serial blood samples or postmortem confirmation was requisite for inclusion of the case. Analysis of the intraventricular conduction defects was made retrospectively from the study of 12 lead electrocardiograms and not from a single monitor lead.

The diagnosis of classic left bundle branch block and right bundle branch block was based on the criteria proposed by the New York Heart Association.[16] The terminology and criteria for conduction defects in left anterior and posterior fascicle were taken from Rosenbaum et al.[2] Left anterior hemiblock was defined electrocardiographically as marked left and superior axis deviation of −45° or more, with Q1–S3 pattern, small R waves in lead II, III and aVF and a QRS duration of less than 0.12 second in the absence of inferior infarction and Wolff-Parkinson-White syndrome. Left posterior hemiblock was recognized when right axis deviation occurred of at least ±110° with S1–Q3 pattern and QRS duration less than 0.12 second in the absence of lateral extension of the infarction and of any apparent cause of right ventricular hypertrophy or extremely vertical heart position. When right bundle branch block was associated with left anterior or posterior hemiblock, the QRS duration was at least 0.12 second.

Diagnosis of incomplete bilateral bundle branch block was made in the presence of the following findings: right or left bundle branch block with a prolonged P–R interval (more than 0.20 second) not due to digitalis, or right bundle branch block with left anterior or left posterior hemiblock. Alternating right and left bundle branch block and left bundle branch block in the standard limb leads with right bundle branch block in the precordial leads was not observed in this series.

The mode of death was classified as sudden or due to progressive "pump" failure. The mechanism of sudden death was recognized as ventricular fibrillation in some patients. When no terminal electrocardiogram was available, the death was considered sudden only when it was unexpected in a patient with an otherwise stabilized condition. Death was attributed to progressive pump failure when the course showed progressive deterioration marked by congestive or hypotensive manifestations.

Statistical analysis for age was performed by 1-way analysis of variance and for mortality by contingency test.

Results

The hospital mortality was 21.2 percent (Table I). This rate is within the range reported earlier from our institution[17,18] and other coronary care units.[19–21]

TABLE I

Incidence and Hospital Mortality

	Total no.	Incidence (%)	Mean Age (yr)	(1 SD)	Deaths no.	Deaths %	Mean Age (yr) at Death	(1 SD)
All patients	212	100	60.5	(11.8)	46	21.2	65.1	(11.4)
Patients with intraventricular conduction defects	51	24	65.4	(10.2)	24	47	66.8	(10.4)
Patients without intraventricular conduction defects	161	76	58.9	(11.7)	22	13.6	64	(10.2)

Incidence and mortality: Intraventricular conduction defects were found in almost 25 percent of the patients (Table I). This compares with 10 to 13 percent of previous reports.[22,23] The mean age of patients with intraventricular conduction defects was higher statistically than that of patients without such defects ($P < 0.01$). The mortality in patients with intraventricular conduction defects was 3.5 times higher than in patients with normal intraventricular conduction ($P < 0.01$). No difference in mean age was found between patients who died with or without intraventricular conduction defects. To dissociate the effect of aging from that of intraventricular conduction defects on mortality the 51 patients having intraventricular conduction defects were matched by sex and age (within 1 year) with 51 patients without intraventricular conduction defects (Table II). Under these conditions, the mortality in the presence of intraventricular conduction defects increased by a factor of 2.5 ($P < 0.01$). The mean age of the patients with intraventricular conduction defects who died was 3 years less than that of those with normal conduction ($P < 0.1$).

TABLE II

Comparative Mortality and Mean Age at Death in Relation to Intraventricular Conduction Defects (Patients Matched for Sex and Age).

	Total no.	Mean Age (yr)	(1 SD)	Deaths no.	Deaths %	Mean Age (yr) at Death	(1 SD)
Patients with intraventricular conduction defects	51	65.4	(10.2)	24	47	66.8	(10.4)
Patients without intraventricular conduction defects	51	65.4	(10.3)	10	19.6	69.7	(7.1)

TABLE III

Analysis of Intraventricular Conduction Defects

			Deaths			
	no.	Incidence (%)	no.	%	Sudden	Progressive Pump Failure
All defects	52*	24	24	47	9	15
LAH	20	9.4	5	25	1	4
Permanent	12		5	...	1 VF	2 CS, 2 CHF
Transient	5		0	...	0	0
+ Transient RBBB†	3		0	...	0	0
RBBB	7	3.3	3	42	1	2
Permanent	5		3	...	1 VF	2 CHF
+ Transient complete A–V block	2‡		0	...	0	0
LBBB	8	3.7	5	63.5	3	2
Permanent	5		5	...	3 VF	1 CS, 1 CHF
Transient	2		0	...	0	0
Incomplete transient	1		0	...	0	0
IBBBB	16	7.5	11	68.7	4 ?	7
RBBB + LAH	9		5	...	2 ?	2 CS, 1 CHF
RBBB + LPH	1		1	...	0	1 CHF
RBBB + P–R > 0.20 sec	2		1	...	0	1 CHF
LBBB + P–R > 0.20 sec	3		3	...	1 ?	1 CS, 1 CHF
RBBB + LPH + P–R > 0.20 sec	1		1	...	1 ?	0
LPH + transient ILBBB	1	0.5	0	0	0	0

* Includes findings of 1 patient listed twice (under incomplete transient LBBB and LPH + transient ILBBB); † also transient IBBBB; ‡ 1 successful temporary transvenous pacemaker.

CHF = congestive heart failure; CS = cardiogenic shock; IBBBB = incomplete bilateral bundle branch block; ILBBB = incomplete left bundle branch block; LAH = left anterior hemiblock; LBBB = left bundle branch block; LPH = left posterior hemiblock; ? = unknown; RBBB = right bundle branch block; VF = ventricular fibrillation.

Table III shows the incidence and the mortality of different types of intraventricular conduction defects. Only the patient who had left posterior hemiblock with transient left anterior hemiblock and incomplete left bundle branch block was classified in 2 different categories.

Left anterior hemiblock: The incidence of left anterior hemiblock, including 3 cases with transient right bundle branch block, was 9.4 percent. The mortality rate of 25 percent is somewhat above the overall mortality of the total series, but not different statistically. Seventeen of the 20 patients with left anterior hemiblock had anterior myocardial infarction, and 6 of these had previous infarction. Inferior location occurred in 2 patients with a previous anterior infarction, and in 1 without previous infarction (Case 4, Table IV). Of these 20 patients with left anterior hemiblock, the pattern was present in 17 on admission, and in 3 it evolved during the postinfarction phase. Of the 17 patients with left anterior hemiblock on admission, normal axis was restored during the period of observation in 3 patients, and in 3 others left axis deviation became much less prominent. Thus, it may be deduced that in this series of 212 myocardial infarctions, left anterior hemiblock occurred as an acute manifestation in only 9 cases (4.3 percent).

Right bundle branch block: Seven patients had isolated complete right bundle branch block (3.3 percent). Among the first 5 patients with acute anterior infarction 4 had this defect before the attack and 2 of them had a clinical diagnosis of pulmonary emphysema. Three of these patients died, and 2 underwent autopsy (Cases 5 and 6, Table IV). In the remaining 2 patients with right bundle branch block, transient complete A–V block developed. In 1 it occurred after acute inferior infarction. When nodal rhythm appeared the right bundle branch block pattern maintained the same contour as during sinus mechanism, which was restored within 24 hours. In the second case, a Mobitz type II phenomenon appeared during acute anterior infarction and preceded ventricular standstill. Temporary pacing was used successfully. Among these 7 patients with right bundle branch block all had a normal frontal plane QRS axis except 1 with pulmonary emphysema who had a QRS axis of 145°.

Left bundle branch block: Five patients had isolated complete left bundle branch block which was permanent, and all 5 died. The pattern was present before admission in 3 and appeared after the infarction in 2. Four had a history of previous infarction. Autopsy was performed in 2 cases (Cases 7 and 8, Table IV). Transient complete left

bundle branch block was observed in 2 patients. Both had an acute anterior infarction with a history of previous infarction, and both survived. Finally, 1 patient had incomplete left bundle branch block accompanied by a transient conduction defect in both left fascicles (Fig. 1). A total of 8 patients had left bundle branch block (3.7 percent). The QRS frontal axis ranged from +30 to −20° in all but the last patient who will be discussed separately.

Bilateral bundle branch block: Among 16 patients with incomplete bilateral bundle branch block, 9 had right bundle branch block with left anterior hemiblock. Five of the 9 died (55 percent), 3 of progressive pump failure and 2 suddenly after transfer from the coronary care unit. Location of the infarction was anterior in 5, undetermined in 1 and inferior in 3. Two of the 3 latter patients had a history of previous infarction, and the third had had a permanent pacemaker inserted 9 months earlier for multiple episodes of Adams-Stokes syndrome. Right bundle branch block with left anterior hemiblock was present during sinus capture at the time the pacemaker was inserted. This patient died of progressive pump failure (Case 10, Table IV).

Only 2 cases of right bundle branch block with left posterior hemiblock were found. Both occurred during anterior infarction. One patient died of cardiogenic shock and asystole the day of admission (Case 11, Table IV); the other, with prolongation of the P–R interval, died suddenly after the coronary care unit stay.

Prolonged P–R interval: An intraventricular conduction defect accompanied by P–R prolongation was found in 6 patients. In the presence of an intraventricular conduction defect, P–R prolongation may be attributed to impaired conduction below the A–V node. This assumption is supported in 3 cases of left bundle branch block in which P–R prolongation appeared concomitantly with left bundle branch block. In the case of right bundle

TABLE IV

Postmortem Findings in 14 Patients with Intraventricular Conduction Defects

Case no.	Intraventricular Conduction Defect	Heart Weight (g)	Coronary Vessels	Heart Muscle
1	LAH	440	Occlusion of LADA by recent thrombus 2 cm from origin	No macroscopic evidence of infarction
2	LAH	450	Severe 3 vessel disease; occlusion of LADA by calcified plaque	Recent extensive anterior infarction
3	LAH	?	2-vessel disease; marked narrowing of LADA; occlusion of RCA 4 cm from origin	Recent extensive septal infarction
4	LAH	410	3-vessel disease; almost complete occlusion of LCA; occlusion of LADA by fresh thrombus	Recent extensive septal infarction
5	RBBB	700	3-vessel disease; occlusion of LADA and LCA	Left and right ventricular hypertrophy. Recent extensive infarction of left ventricular wall; (emphysema present)
6	RBBB	450	3-vessel disease; occlusion of LADA by thrombus 2 cm from origin	Recent extensive anterior and septal infarction
7	LBBB	340	3-vessel disease, more pronounced in LCA and LADA	Recent subendocardial necrosis of posterolateral and anterior wall
8	LBBB	430	3-vessel disease; double LADA, the right branch occluded at its origin and patent left branch; LCA poorly developed; RCA occluded by thrombus 1.5 cm from origin	Recent extensive infarction of septum from apex to base
9	RBBB + LAH	390	Occlusion of LADA by thrombus at origin	Recent extensive anteroseptal infarction.
10	RBBB + LAH	610	3-vessel disease; severe narrowing of LADA and LCA; severe proximal narrowing of RCA	Recent infarction of inferior and posterior wall
11	RBBB + LPH	450	3-vessel disease; severe narrowing of LADA and RCA	Recent infarction of entire septum extending into left ventricular wall
12	LBBB + P–R > 0.20 sec	550	3-vessel disease; occlusion of main left coronary artery by calcified atheroma; occlusion of distal RCA	Organized infarction at apex Organizing infarction of inferior wall involving posterior part of septum
13	LBBB + P–R > 0.20 sec	500	3-vessel disease; peripheral occlusion in territory of the 3 vessels	Extensive infarction of most of left ventricle
14	RBBB + LPH + P–R > 0.20 sec	500	3-vessel disease; proximal occlusion of LCA; severe narrowing of RCA and LADA	Several areas of old infarction with fibrous scarring in posterior and anterior wall extending in septum; recent infarction in apex of left ventricle

LADA = left anterior descending artery; LAH = left anterior hemiblock; LBBB = left bundle branch block; LCA = left circumflex artery; LPH = left posterior hemiblock; RBBB = right bundle branch block; RCA = right coronary artery.

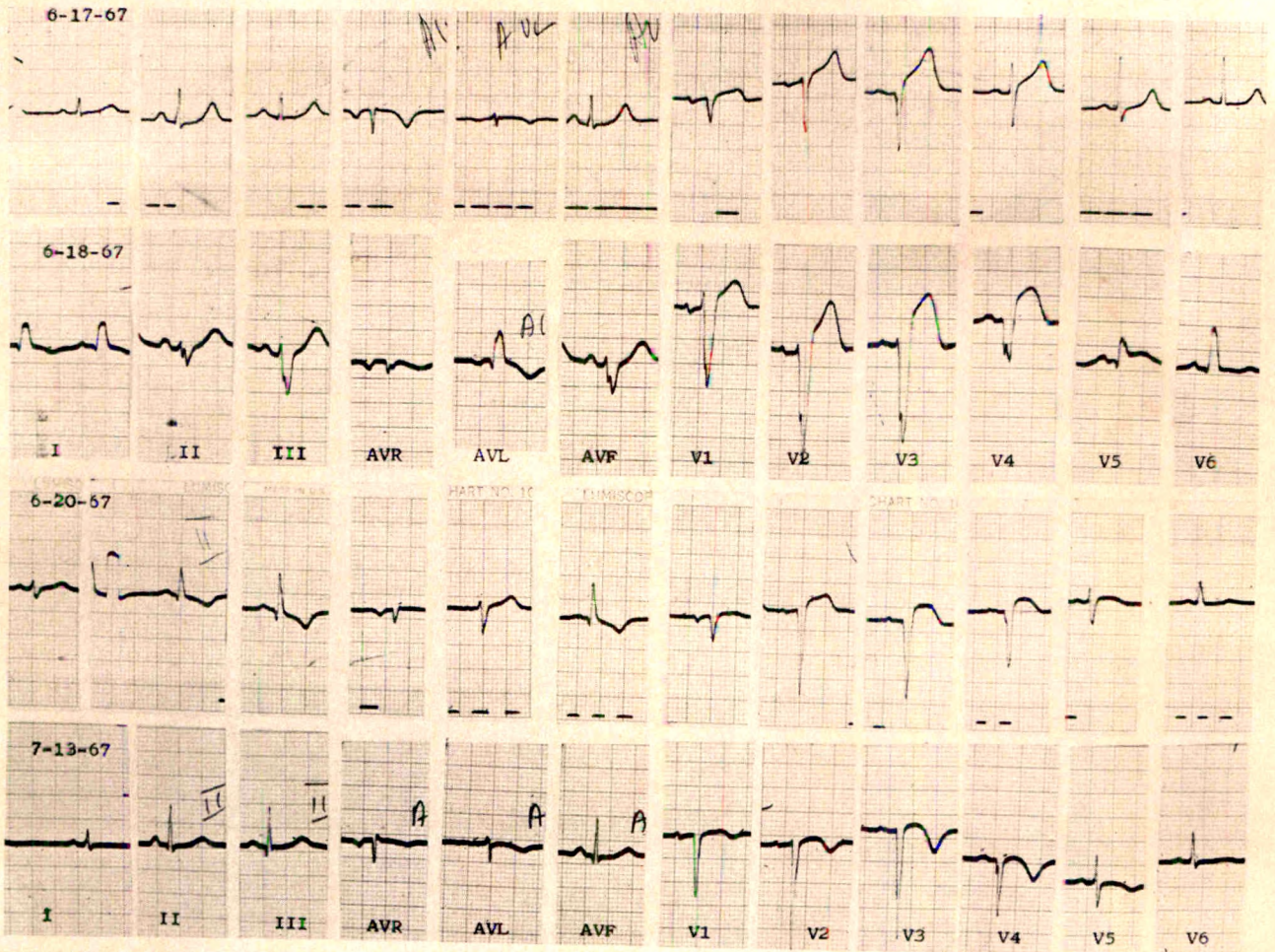

Figure 1. Electrocardiogram taken early during acute anterior infarction on June 17, 1967 (**first row**) showing sinus rhythm, normal P–R interval, ΔQRS +60° and QRS duration of 0.08 second. On June 18 (**second row**) the tracing suggests left anterior hemiblock with incomplete left bundle branch block. On June 20 (**third row**) left posterior hemiblock is present and decreases in degree on the last electrocardiogram taken on July 13 (**fourth row**).

branch block with left posterior hemiblock, differences in the P–R interval were accompanied by variations in QRS contour. In 2 cases of right bundle branch block, P–R prolongation was not digitalis-dependent. One of these patients had had transient left anterior hemiblock 7 years earlier. The mean QRS axis of left bundle branch block with P–R prolongation ranged from +10 to −10°. Mean QRS axis of the right bundle branch block with P–R prolongation was +30°. Mean QRS axis of right bundle branch block with left posterior hemiblock was +140°. Five of 6 patients with intraventricular conduction defects and P–R prolongation died, 3 of progressive pump failure and 2 suddenly after the coronary care unit stay.

Left posterior hemiblock: The last case listed in Table III, diagnosed as left posterior hemiblock, merits further comment. This 65 year old man with an acute anterior infarction (Fig. 1) had no previous history of arteriosclerotic heart disease and no evidence of hypertension. On admission the QRS duration was normal, and the QRS axis was +60°. The following day the frontal plane QRS axis was −50°. The tracing met the criteria for left anterior hemiblock. However, the QRS duration of 0.12 second was longer than that expected from the left anterior hemiblock alone. According to Rosenbaum,[2] widening of the QRS interval in presence of left anterior hemiblock may be explained by an "infarction block" between the left posterior and the left anterior Purkinje networks. An alternative explanation might be an additional delay in conduction in the main bundle. We favor the second explanation because the transient nature of this impairment of conduction is more likely to be a result of ischemia in the conductive tissue rather than extensive necrosis of the cardiac muscle. Left anterior hemiblock with incomplete left bundle branch block disappeared 2 days later, and the frontal QRS axis shifted to +110°. The initial 0.02 second vector was directed quite differently. It has a left and superior orientation, inscribing a small 0.20 second Q wave in inferior leads and a small R wave in lead aVL. The 0.06 second vector was oriented inferiorly and to the right giving an S wave in aVL and a taller R_3 than R_2. The QRS loop was clockwise. Although the QRS duration was shorter, the QRS pattern was the mirror image of that taken 2 days earlier. The evolutionary pattern of successive electrocardiograms in this man of upper middle age, who had an acute myocardial infarction and no electrocardiographic evidence of right ventricular hypertrophy and no evidence of

pulmonary disease, makes the diagnosis of residual left posterior hemiblock quite definite. The last electrocardiogram of Figure 1, in which the main QRS axis returned to 90°, makes it obvious that the diagnosis of delayed conduction in the left posterior fascicle cannot be made from an isolated tracing.

Pathologic findings: The presence of an intraventricular conduction defect in arteriosclerotic heart disease with acute myocardial infarction is indicative of extensive involvement of the coronary tree, as can be seen from the data of 14 autopsy cases in Table IV.

Three-vessel disease was found in 12 cases. Only 2 patients had evidence of arteriosclerosis limited to the left coronary artery system. These patients had left anterior hemiblock (Cases 1 and 3). Recent occlusion of one or more vessels was found in 11 instances. In the other 3 patients severe generalized narrowing was seen in the major arteries. Recent infarction was confirmed by microscopic examination in all patients. Although it was not evident by gross examination in Case 1, extensive damage was obvious in the other 13 cases. The septum was extensively involved by the necrotic process in 8 instances. The weight of the heart tended to be greater and old lesions with scarring throughout the muscle were more often seen associated with the fresh infarction in patients with incomplete bilateral bundle branch block.

Discussion

The increased frequency of intraventricular conduction defects in myocardial infarction is explained primarily by the recognition of left anterior hemiblock. Because of its unique blood supply from septal branches of the anterior descending artery and its delicate structure, the left anterior fascicle is highly vulnerable to ischemic or necrotic processes. As a result, left anterior hemiblock was the most common intraventricular conduction defect associated with myocardial infarction.[8] In addition to being the most common defect, left anterior hemiblock appeared to be the most innocuous.

The second most frequent type of intraventricular conduction defect is the association of right bundle branch block and left anterior hemiblock. The middle segment of the right bundle branch is incorporated within the muscular ventricular septum and shares the blood supply from the anterior descending coronary artery with the left anterior fascicle.[24] It has been shown to be the most frequently injured portion of the right bundle branch in coronary artery disease.[1,5] Therefore, the frequent association of right bundle branch block and left anterior hemiblock in coronary artery disease seems to be due to the interruption of the frequently diseased common blood supply rather than to the intimate relation of the structures in their proximal segment. In fact, the proximal segment of the right bundle branch derives its blood supply from branches of the A–V nodal artery and, therefore, from the right coronary artery in 90 percent of human hearts.[7,24] In most observations of the sequential development of this bifascicular block, left axis deviation precedes the appearance of the right bundle branch block,[2,25] although the reverse sequence has been reported.[9,10] The high mortality in this bifascicular block suggests that it occurs in presence of extensive myocardial damage. A further risk is the propensity for complete heart block to develop.[9,11]

Both incidence and mortality rates of complete right bundle branch block were lower in our series than in others.[22,23] This is explained by the inclusion in earlier studies of bifascicular block (right bundle branch block with left anterior hemiblock) in the right bundle branch block category. However, it is important to recognize that even isolated right bundle branch block in the presence of myocardial infarction has consistently higher mortality rates than normal intraventricular conduction.

Complete left bundle branch block in acute myocardial infarction has a poor prognosis because its presence implies, at best, 2-vessel disease. The sudden development of complete left bundle branch block, whether permanent or intermittent, suggests impairment of the blood supply to the main bundle. This arises predominantly from the right coronary artery and from branches of the left anterior descending artery.[7] The frequent pathologic correlation of complete left bundle branch block and 2-vessel ischemic disease with injury to the main bundle has been documented.[6] These observations apply in myocardial infarction and do not pertain to conduction defects due to skeletal factors as in Lev's disease[24] or to idiopathic factors as in Lenegre's disease.[26] In addition, Unger et al.[27] have pointed out the vulnerability of the relatively compact proximal fibers of the main left bundle to a discrete lesion compared to that of the more distal ramifications. Therefore, as expected from anatomic considerations, complete left bundle branch block due to postdivisional injuries to the left posterior and anterior fascicles individually should be rare. Such a situation might imply 3-vessel disease and might be suspected clinically by the intermittent appearance of left anterior and left posterior hemiblock preceding the development of complete left bundle branch block. However, such a case has never been described.

The posterior division of the left bundle branch seems relatively invulnerable to coronary artery disease. Although the first to separate from the bundle of His, the left posterior fascicle has the shortest pathway to the angle of the interventricular septum and the posterior wall and has the largest diameter of the 3 fascicles.[1,24] In addition, it has a double blood supply from the anterior and posterior descending arteries.[1] Only 1 previous case of isolated left posterior hemiblock confirmed by pathologic study of the conduction system has

been reported.[4] The complete finding of "pure" left posterior hemiblock is usually found when conduction defects in other fascicles are intermittent, primarily in the right bundle branch.[28,29] The sequence of left anterior hemiblock followed by left posterior hemiblock in the electrocardiograms presented in Figure 1 is uncommon.

The low incidence of right bundle branch block with left posterior hemiblock[8,10,12] results from the rare interruption of the left posterior fascicle, in conjunction with separate lesions affecting the right bundle branch. The very high mortality experienced with this bifascicular block illustrates the necessary presence of an extensively diseased coronary tree. Among the bifascicular blocks, the combination of right bundle branch block with left posterior hemiblock has been reported to have the highest propensity for development of complete heart block.[2,12,14]

Clinical significance: In acute myocardial infarction, intraventricular conduction defects have an unfavorable effect on in-hospital survival. This is true whether the conduction disturbance existed before infarction or occurred acutely during infarction. A spectrum of intraventricular conduction defects may be defined. At the most benign part of the spectrum is isolated left anterior hemiblock not associated with QRS prolongation. The prognosis becomes progressively more ominous in complete right bundle branch block, complete left bundle branch block and, finally, in incomplete bilateral bundle branch or bifascicular block. The more extensive the intraventricular conduction abnormality, the greater the propensity to progressive pump failure and sudden death. The high mortality rates in patients with acute myocardial infarction and intraventricular conduction defect are not age-dependent.

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Aberrancy of Junctional Escape Beats

Evidence for Origin in the Fascicles of the Left Bundle Branch

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The mechanism of aberrancy of so-called atrioventricular (A–V) junctional escape beats was investigated in 8 cases, in 5 of which His bundle electrography was performed with both conducted and escape beats recorded. Aberrancy in junctional beats usually shows features of incomplete or complete right bundle branch block and leftward or rightward shift of the QRS axis in the frontal plane. From the morphologic point of view the aberrancy resembles that seen in conducted beats with the additional feature of bifascicular block. Functional aberrancy based on incomplete recovery of the conduction fibers cannot account for aberrancy in slow junctional rhythms. Phase 4 depolarization may explain the aberrancy in slow heart rates but cannot readily account for the fusion complexes so frequently seen in these rhythms. His bundle electrography in the present study showed a time relation between His spikes and the onset of the QRS complex which excludes the possibility of antegrade conduction of the aberrant beats along the same pathway used by descending sinus beats as well as true junctional beats descending through the main His bundle. Specifically, the His spikes were found at or near the onset of the QRS complexes in aberrant escape beats, whereas they were ahead of the QRS complexes by the expected interval of 40 to 50 msec in the conducted beats. This temporal relation favors propagation of escape impulses from their origin bidirectionally, that is, simultaneously toward the ventricular myocardium and retrograde toward the main His bundle. This observation, together with the right bundle branch block and the axis deviation, places the escape focus in 1 of 2 fascicles of the left bundle branch: in the superior division for beats displaying right axis deviation and in the inferior division for beats displaying left axis deviation. With acceptance of a fascicular origin for these beats, a satisfactory explanation becomes readily available for the fusion complexes.

When heart rate slows because of atrioventricular (A–V) block or sinus bradycardia, an escape focus usually emerges and drives the ventricle for one or more cycles. It is generally accepted that the escape beats arise in the A–V junction or within the ventricles producing narrow or wide QRS complexes, respectively. Quite frequently, however, escape QRS complexes are not entirely identical with those of conducted beats and yet are not sufficiently wide and bizarre to justify a diagnosis of ventricular origin. The abnormality in such escape beats commonly appears in the form of minimal increases in the width of the QRS complex together with shifts of its mean axis. Therefore, such altered beats have been thought to originate within the A–V junction but to propagate to the ventricles in an aberrant fashion.[1–4]

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TABLE I

Eight Cases of Escape Rhythm

Case no.	Age (yr) & Sex	Diagnosis	Digitalis	A–V Conduction Delay
1	89F	CHF, cause?; acute anterior MI	? Toxicity	No
2	73M	Acute diaphragmatic MI	No	No
3	53M	Acute anteroseptal MI	No	No
4	66M	Multiple MI	No	No
5	65F	Shock, cause?	No	No
6	15M	Subarachnoid hemorrhage	No	No
7	55F	Ischemic heart disease	Toxicity	Yes
8	75F	Ischemic heart disease	Yes	Yes

CHF = congestive heart failure; MI = myocardial infarction.

Because the most common mechanism of QRS aberrancy—namely, incomplete recovery of the intraventricular conduction pathways by virtue of short coupling intervals or long preceding cycles—cannot be incriminated in escape aberrancy,[4] other mechanisms have been sought. The few authors who have given thought to the problem have been unanimous in suggesting preferential conduction of A–V junctional impulses in part or totally along accessory paraspecific pathways.[1–4] Kistin[4] did consider spontaneous phase 4 depolarization, originally described by Singer et al.,[5] but believed that the presence of fusion beats was contradictory to this explanation.

In this communication evidence will be presented to indicate that in many cases of so-called junctional escape aberrancy, impulses originate in the fascicles of the left bundle branch and, therefore, propagate within the ventricles in an abnormal yet predictable fashion. The finding of a fascicular origin for the escape beats provides a readily acceptable explanation for the abstruse problem of fusion of a supposed junctional beat with a simultaneously descending sinus beat using the same path.

Material and Methods

Eight cases of escape rhythm were studied, and His bundle electrography for both escape and conducted beats was carried out in 5 cases. The origin of the escape rhythm was localized in the fascicles of the left bundle branch in 5 cases and in the true A–V junction above the bifurcation in the remaining 3. The latter 3 cases were included for clarification of points useful in the differential diagnosis of various types of escape rhythm. The pertinent biographic and clinical data are presented in Table I.

Patients were brought to the laboratory for study because of the arrhythmia. His bundle potentials were recorded by the method of Scherlag et al.[6] employing a bipolar pacemaker catheter and a percutaneous femoral vein approach. Intraatrial potentials were recorded by means of a second bipolar catheter introduced through the same vein or an arm vein. Recordings were made on an Electronics for Medicine photographic recorder, model DR-8, at paper speeds of 100 to 200 mm/sec. Measurements of intervals in relation to the His bundle spike were made using a Gerber variable scale, model TR007100B. P–His and His–Q intervals were measured using the earliest visible parts of the P and QRS in surface electrocardiographic leads. The atrial and ventricular potentials recorded on the His electrogram were not used because they represent depolarization of atrial and ventricular myocardium closest to the catheter electrode and do not correspond to those segments of the myocardium which are first to depolarize.

Results

P–His, His–Q, P–R and QRS intervals and the prevailing rates are presented in Table II. In the 2 cases of true junctional rhythm originating above the bifurcation (Cases 7 and 8), His–Q intervals for descending sinus beats and for escape beats were exactly the same, and the QRS complexes were identical, indicating passage of impulses

TABLE II

Various Intervals (msec) and Rates

	P–His		His–Q		P–R		QRS		QRS Configuration and Axis		Rate	
Case no.	Normal Sinus	Escape	Normal Sinus	Escape	Normal Sinus	Escape	Normal Sinus	Escape	Normal Sinus	Escape	Normal Sinus	Escape
1	160	...	45	−5	200	...	75	95	N +15°	IRBBB +150°	100–110	70–80
2	140	...	35	−5	175	...	80	110	N −30°	IRBBB −75°	60–82	58–60
3	140	...	40	0	180	...	85	110	N +75°	IRBBB +85°	70–75	58–62
4	ND	ND	ND	ND	180	...	70	90	N +45°	IRBBB +90°	42–45	30
5	ND	ND	ND	...	A Fib	A Fib	70	90	N +55°	IRBBB −45°	70–90	66
6	ND	ND	ND	ND	130	...	70	95	N +60°	ILBBB +90°	42–66	50
7	145–300	...	70	70	220–370	...	90	90	N +30°	N +30°	45–50	62
8	205	...	50	50	255	...	100	100	IRBBB +75°	IRBBB +75°	29	44

A Fib = atrial fibrillation; ILBBB = incomplete left bundle branch block; IRBBB = incomplete right bundle branch block; N = normal; ND = not done.

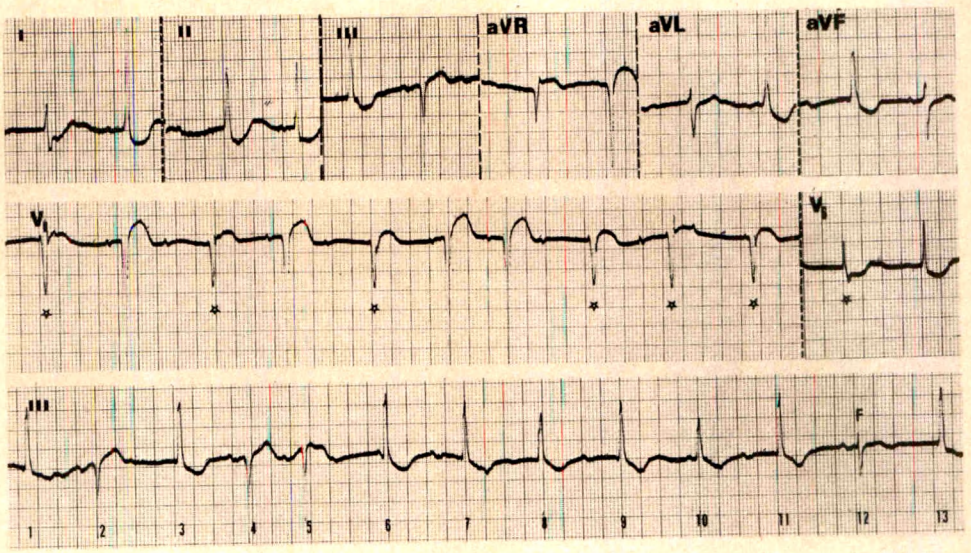

Figure 1. Case 1. Limb leads in top panel show an escape beat and a conducted sinus beat in each lead. Escape beats exhibit marked right axis deviation and incomplete right bundle branch block. Rhythm strips V_1 and III in middle and bottom panels (see text for explanation).

along the same antegrade pathways, namely, His bundle-bundle branches-Purkinje fibers. In sharp contrast, in the cases of fascicular rhythm (Cases 1 to 3) His–Q intervals for escape beats were much shorter than those of conducted sinus beats. In fact, the His spikes in the fascicular beats occurred at or shortly after onset of the QRS complexes, clearly indicating an abnormal reversed direction of the activation process. Retrograde conduction to the atria was not present in any of the fascicular beats because of the coexistent but independent activity of the sinus mechanism.

Analysis of Electrocardiograms and His Electrograms

Case 1: Figure 1 shows selected leads taken from an 89 year old woman with congestive heart failure, acute anterior myocardial infarction and possible digitalis toxicity. In each of the leads, I, II, III, aVR, aVL, aVF and V_6, the first beat is an escape beat and the second is of normal sinus origin. The atrial rate is over 100 beats/min. A–V conduction is impaired, with many blocked P waves, after which escape beats marked by asterisks appear. In the conducted beats, QRS complexes are 0.075 second in duration and have a frontal plane axis of +15°. Escape beats are slightly wider, 0.095 second, but exhibit a marked right axis deviation of +150°. In lead V_1, the small late positive deflections indicate the additional feature of incomplete right bundle branch block. The rhythm strip of lead III at the bottom shows a continuous run of escape rhythm extending from beats 6 to 11 at a rate of 75/min. Beat 12 is a fusion complex. According to the prevailing views, this escape rhythm would be considered of junctional origin with the additional feature of intraventricular aberrancy. Ventricular escape in the classic sense would not be a tenable diagnosis because of the absence of very wide, bizarre QRS complexes.

Figure 2 shows His bundle potentials recorded simultaneously with leads aVL, II and V_1. The first and third beats are conducted sinus beats, and beat 2 is an escape beat of the same type shown in Figure 1. In the sinus beats the sequence of atrium-His-ventricle is preserved, and the P–His and His–Q intervals of 160 and 45 msec, respectively, indicate normal antegrade conduction. In beat 2 the His deflection is clearly visible just before the ventricular potentials, but the temporal relation between the His spike and the QRS complex is grossly abnormal. The His spike appears 5 msec after onset of the QRS. From its origin, the escape impulse must have propagated in 2 opposite directions and reached the myocardium and the His bundle almost simultaneously. Assuming equal velocity of conduction in both directions, and keeping in mind the total His–Q time of 45 msec, the origin of the escape beats can be located at a distance of 25 msec from the His bundle and 20 msec from the ventricular myocardium. Roughly, this site would correspond to one of the

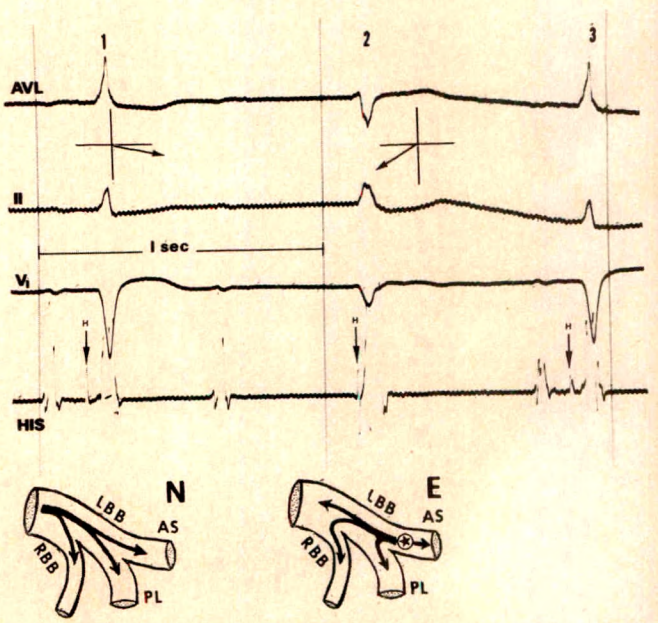

Figure 2. Case 1. His bundle recording with leads aVL, II and V_1 showing normal H–Q interval in sinus beats (1 and 3) and almost simultaneous excitation of His bundle and ventricles in escape beat (2) with right axis deviation and incomplete right bundle branch block. Proposed origin of escape beat is shown in diagram E.

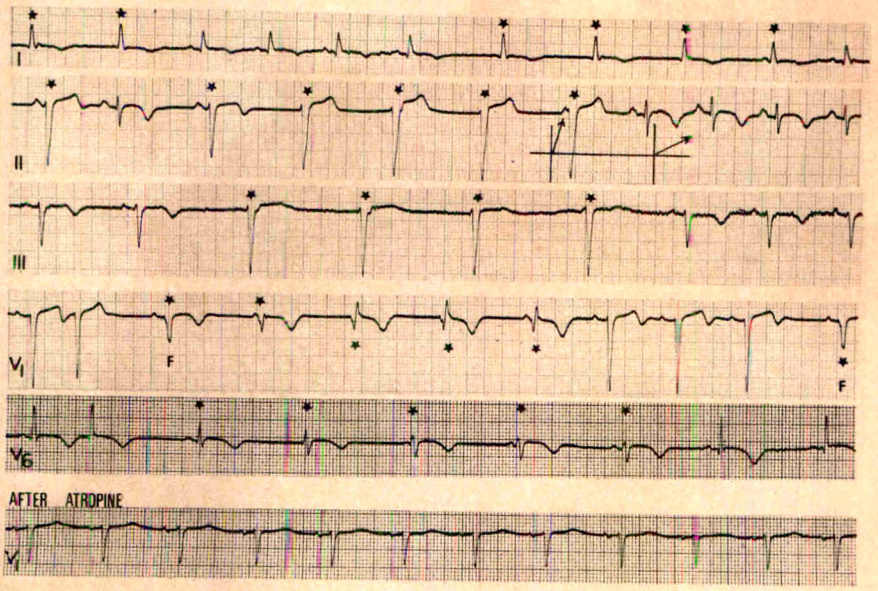

Figure 3. Case 2. Selected limb and precordial leads showing escape beats (asterisks) with incomplete right bundle branch block and right axis deviation.

fascicles of the left bundle. The presence of incomplete right bundle branch block together with right axis deviation in this escape beat is reminiscent of the bifascicular block caused by delayed activation in the right bundle and the inferior division of the left bundle. Study of the diagrams below the His electrogram, one belonging to normal sinus beats (N) and the other to escape beats (E), shows that an impulse originating within the superior fascicle of the left bundle (asterisk) would reach the right bundle and the inferior division sufficiently late to mimic the pattern of intraventricular aberrancy of a descending beat.

Case 2: In this 73 year old man with acute diaphragmatic myocardial infarction a marked sinus arrhythmia occurred, and during the periods of sinus slowing an escape mechanism became active (Fig. 3). Escape QRS complexes were 0.11 second wide and displayed right bundle branch block and marked left axis variation. Injection of 1 mg of atropine sulfate intravenously accelerated the sinus mechanism and eliminated the escape rhythm. The third and last beats in lead V_1 and several other beats in the entire tracing are fusion complexes.

In Figure 4, His bundle potentials for 2 normal beats in the left panel and 2 escape beats in the right panel show that the His–Q relation is grossly abnormal in the escape beats. The His spikes occur 5 msec after the onset of QRS. The presence of right bundle branch block and the marked left axis deviation place the escape focus in the inferior division of the left bundle branch as shown in the accompanying diagram.

Case 3: In this case (Fig. 5), sinus arrhythmia occurred during the early stages of an acute anteroseptal myocardial infarction, and slowing of the sinus rate to less than 60 beats/min activated an escape mechanism in which the QRS complexes were 0.11 second wide and possessed features of incomplete right bundle branch block and an indeterminate frontal plane QRS axis which was probably 10° to the right of the axis for

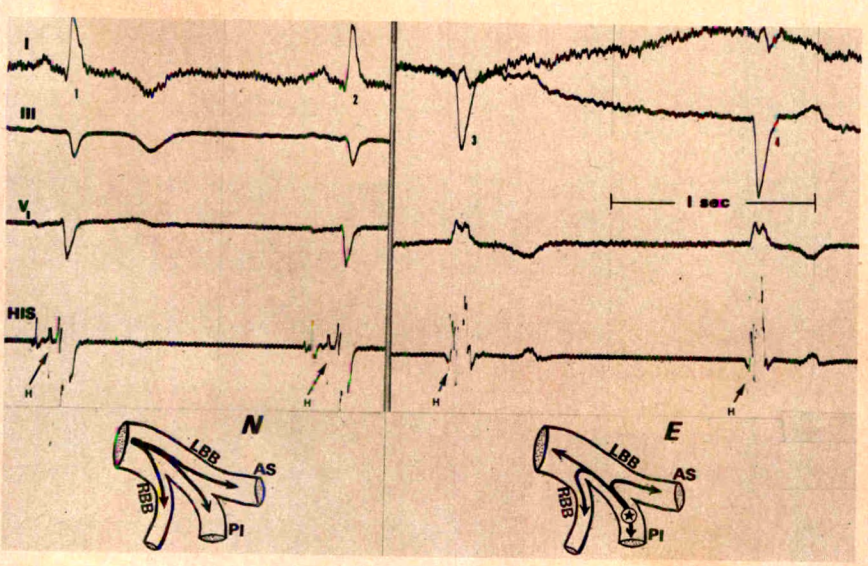

Figure 4. Case 2. His bundle recordings in sinus beats (1 and 2) and escape beats (3 and 4) (see text).

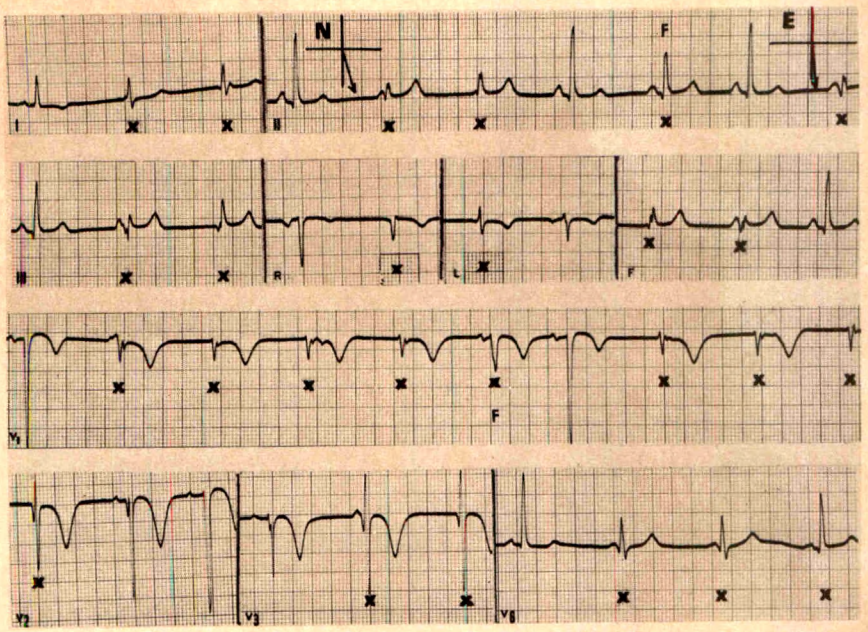

Figure 5. Case 3. Limb leads and selected chest leads showing escape beats (X) and fusion beats (F).

conducted sinus beats. Fusion complexes can be seen in most of the leads but are most conspicuous in leads II (fifth beat) and V_1 (sixth beat).

In Figure 6, His bundle electrograms together with lead V_1 are shown for 2 conducted sinus beats (1 and 2) and 4 escape beats (3 to 6). The His–Q interval of 40 msec for the normal beats compares with a His–Q interval of 0 msec in escape beats, indicating that from its origin the escape beat simultaneously reaches the His bundle and the ventricular myocardium. This observation, and the fact that a conspicuous axis shift is not seen in escape beats, suggests a site of origin within the penetrating portion of the left bundle just before its branching or within the superior fascicle near the penetrating portion of the main left bundle.

Case 4: Rhythm strips (Fig. 7) of this 66 year old man with multiple old myocardial infarctions show sinus bradyarrhythmia with aberrantly conducted escape beats marked by asterisks. Escape beats show features of incomplete right bundle branch block and right axis deviation of +90°. His bundle electrography had not yet been developed, and the localization of the escape focus in the superior division of the left bundle branch shown in the accompanying diagrams is presumptive and based on the same arguments marshalled in the previous cases.

Case 5: This 65 year old woman entered the hospital in a state of shock, probably septic in origin. The electrocardiogram (Fig. 8) showed atrial fibrillation with a perfectly regular ventricular rhythm at a rate of 66/

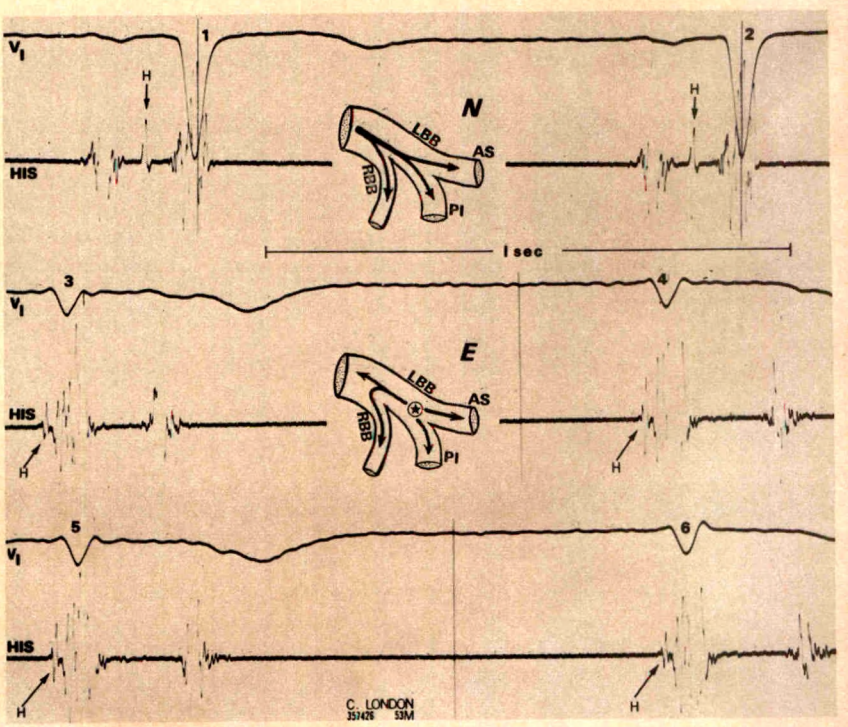

Figure 6. Case 3. His bundle recording with lead V_1 showing conducted sinus beats (1 and 2) and escape beats (3 to 6).

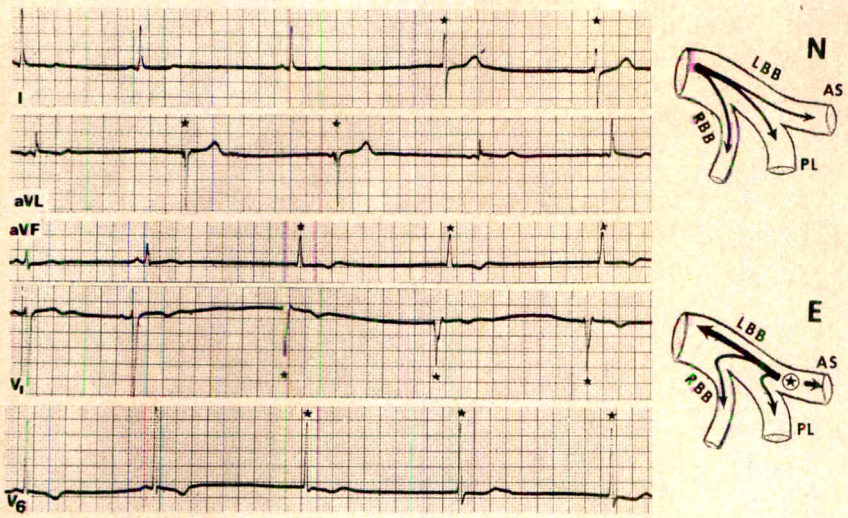

Figure 7. Case 4. Rhythm strips showing normal sinus beats and aberrantly conducted escape beats (asterisks).

min (Section A). The QRS complexes had features of incomplete right bundle branch block and left axis deviation of −45°. Another tracing taken 30 minutes later showed resumption of atrioventricular conduction with periods of 2 or more conducted beats seen in leads I, II, III, V_1. The first 6 beats in V_4 are conducted beats, whereas the last 2 beats are of the escape variety. The conducted beats are irregular and narrow, whereas the escape beats are regular and slightly wider. The origin of the escape beats was localized in the inferior fascicle of the left bundle. Unfortunately, the patient did not live long enough for further studies.

Discussion

In 1938, Katz and Kaplan[7] in describing 4 cases of "unusual A–V nodal rhythms" illustrated a case in which junctional escape beats differed from conducted sinus beats in that the former had a monophasic R wave whereas the latter had RS complexes. However, no attempt was made to explain this change of QRS axis. A similar phenomenon was again noted briefly in 1950 by Hwang and Langendorf.[8] These investigators observed slight alterations in QRS configuration of "A–V nodal escape" beats in 1 of 25 cases of escape rhythm in the presence of atrial fibrillation. They suggested that the morphologic difference represented aberrancy and not a ventricular origin. Pick[1] in 1956 was the first to discuss the matter of aberrancy of junctional escape beats and studied 11 such cases. Because prematurity and inadequate recovery did not apply, Pick ruled out functional explanations in search of anatomic ones and suggested preferential conduction of junctional escape beats along paraspecific A–V pathways of the type demonstrated by Mahaim[9] and later by Lev and Lerner.[10] These workers had shown specialized conduction fibers to extend from the A–V node or main His bundle to the myocardium of the interventricular septum. The presence of fusion complexes in 1 other case was accepted by Pick as evidence for the ventricular origin of the escape beats. Goodman

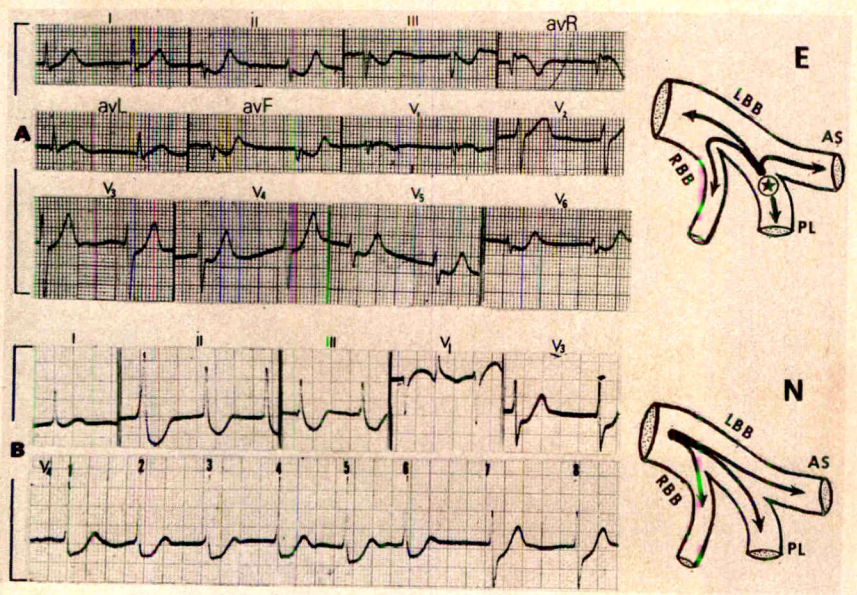

Figure 8. Case 5. Twelve lead electrocardiogram (A) showing atrial fibrillation and escape rhythm. Panel B shows sinus and escape beats.

and Pick[2] in 1961 published an interesting case of rheumatic carditis in which junctional escape beats were grossly aberrant in configuration but not much wider than conducted beats; in addition, there was a profusion of fusion forms. Accepting the thesis that fusion cannot result from impulses traveling in the same direction and using the same pathway, Goodman and Pick concluded that the escape beats must have used certain paraspecific pathways or that they originated in the interventricular septum midway between the 2 bundle branches. They admitted that they could not decide between these 2 possibilities but favored the former. Walsh[3] also discussed the question of aberrancy of junctional beats over a wide range of rates from 50 to 100 beats/min. He did not exclude a ventricular origin but suggested that the relatively rapid rates favored a higher pacemaker. Walsh also stressed the high frequency of fusion complexes and suggested conduction along Mahaim's paraspecific pathways. He did not favor an origin within the interventricular septum because such beats should propagate within the ventricles in similar fashion and produce similar QRS complexes in various persons.

Kistin's report[4] of 6 cases of aberrancy of junctional beats is by far the most thoroughly documented paper on the subject. Using esophageal leads for the study of timing and direction of the retrograde P waves situated adjacent to the QRS of aberrant escape beats, he observed that the very short R–P′ intervals favored a junctional focus and excluded ventricular escape mechanism. Consequently, he suggested that aberrancy and fusion of junctional beats can best be explained by assuming conduction into the ventricles by pathways other than the usual A–V pathways. Kistin did not consider the spontaneous phase 4 depolarization and the resultant low membrane potential described by Singer et al.[5] a good explanation for aberrancy of junctional beats because it did not provide a simultaneous explanation for the fusion complexes. It appears to us that if phase 4 depolarization which is likely to occur toward the end of long diastolic cycles were responsible for the aberrancy, then the incidence of such aberrancy would have to be the same in sinus bradycardia as in slow junctional rhythms. However, aberrancy in sinus bradycardia is extremely rare,[11] although it is a relatively common observation in junctional beats.

Fascicular origin of escape beats: If aberrancy in so-called junctional escape beats cannot be ascribed either to incomplete recovery or to phase 4 diastolic depolarization, then an anatomic origin must emerge as a more tenable explanation. Our finding of His spikes at or near the beginning of the escape QRS complexes excludes the possibility of a descending impulse traversing the main His bundle before reaching the ventricular myocardium. Comparison of His–Q intervals in conducted sinus and junctional beats suggests origin of impulses at some point equidistant between the main His bundle and the Purkinje fibers. This localization is consistent with the fascicles of the left bundle branch. The recent studies of Lau et al.[12] and of Narula et al.[13] concerned with recording of left bundle potentials in dogs and in man, respectively, support our finding that in beats originating from the left bundle, the impulse travels retrograde to reach the main His bundle. Activation of the main His bundle is therefore delayed and brought closer to the ventricular potentials. The marked alterations of QRS axis which have featured prominently in most of the reported cases of escape aberrancy and in the cases described herein are in keeping with the origination of the impulse in 1 of the 2 fascicles, reaching the other fascicle a little later, thus masquerading as the familiar fascicular block in conducted sinus beats. The incomplete, rather than complete, right bundle branch block, so common in such beats, is also to be expected. An impulse originating in a fascicle of the left bundle would require, according to observations reported here and the studies of Narula et al.,[13] 15 to 20 msec to reach the myocardium of the left ventricle and about the same period of time to arrive at the bifurcation. Each impulse would begin its descent along the right bundle branch at about the time that it reaches the myocardium of the left ventricle. Allowing 20 to 25 msec for the impulse transmission through the right bundle and its Purkinje network, one can readily see that activation of the right ventricular myocardium would lag behind that of the ventricle by 20 to 25 msec. This modest time difference between the 2 ventricles would cause the pattern of incomplete instead of complete right bundle branch block. This calculated time difference corresponds with the increments of QRS duration from conducted to escape beats observed in this study and shown in Table II.

The localization of impulses in the fascicles offers a ready explanation for the fusion process often noted. In fact, from this viewpoint, fascicular beats do not differ materially from classic idioventricular beats. We have observed no examples of escape beats originating in the right bundle with resultant left bundle branch block. However, there is no reason why such beats could not occur.

Differential Diagnosis

Bradycardia-dependent aberrancy in junctional escape beats: Figure 9 (Case 6) is believed to depict an example of the rare phenomenon of aberrancy due to phase 4 depolarization in true junctional beats arising above the bifurcation. Escape beats, some of which are marked by X, show a rightward shift of the QRS axis and loss of the R waves in leads V_1 and V_2 consistent with incom-

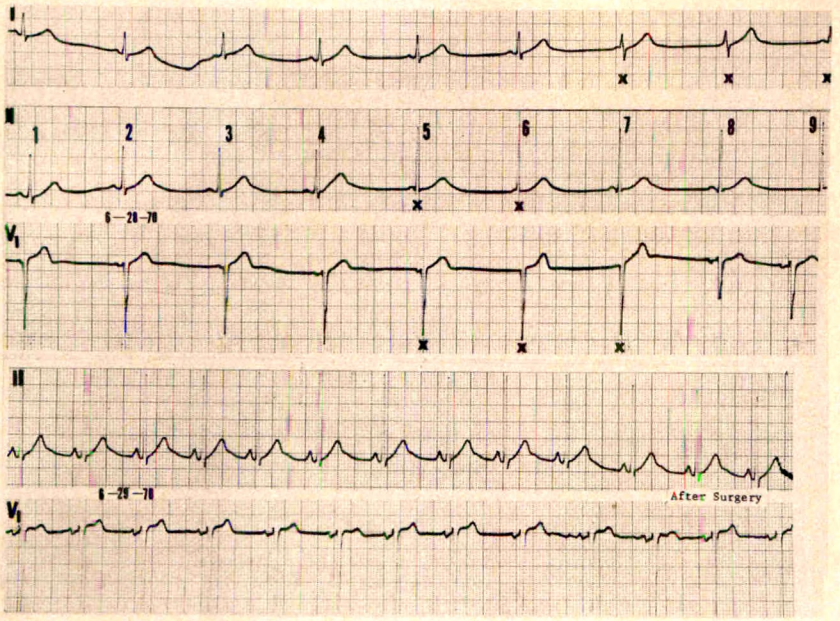

Figure 9. Case 6. Selected rhythm strips showing sinus beats and escape beats (marked X).

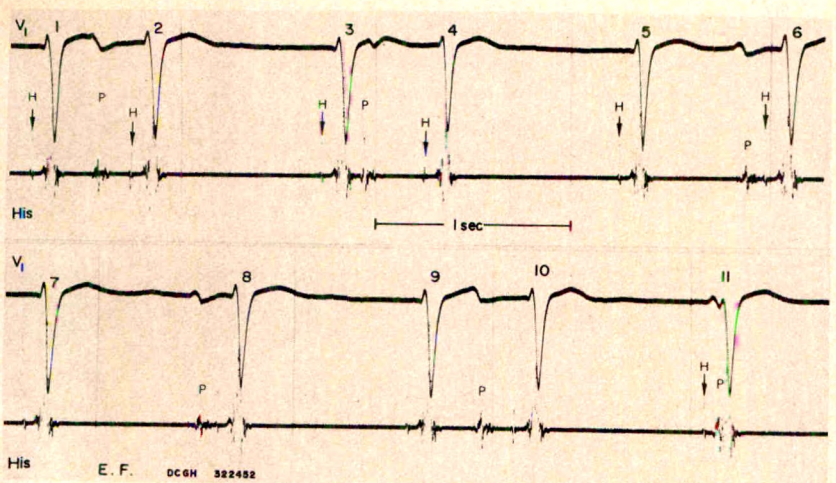

Figure 10. Case 7. His bundle recording and lead V_1 showing true junctional escape beats (3,5,7,9,11) with His–Q interval identical to that of conducted sinus beats (2,6,8,10).

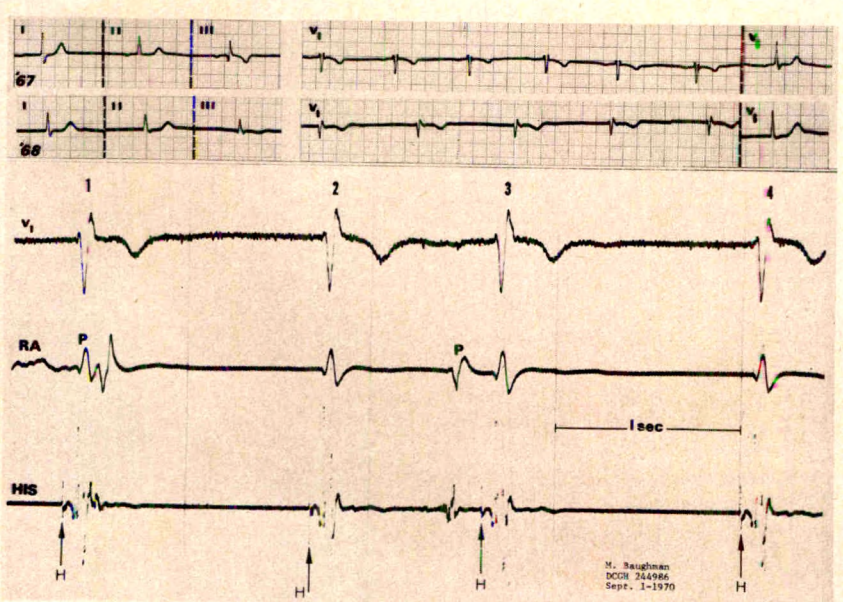

Figure 11. Case 8. **Top,** selected leads of previous tracings. **Bottom,** His bundle recording with V_1 and right atrial lead (RA) showing aberrantly conducted junctional beats (2 and 4) due to preexistent conduction impairment of right bundle branch as seen in sinus beats 1 and 3, and also in tracings of 1967 and 1968. Note that the His–Q intervals are the same for conducted and escape beats.

plete left bundle branch block. The combination of right axis deviation and incomplete left bundle branch block is consistent only with conduction delay in the inferior division of the left bundle in case of a descending beat. To ascribe the right axis deviation to origin of the impulse from the superior division of the left bundle would demand the coexistence of an incomplete right bundle branch block which is conspicuously absent in this case.

Ventricular escape rhythms: Such escape rhythms at slow rates and also at rates very near the prevailing sinus rate (accelerated isorhythmic ventricular rhythm)[14] are relatively common in acute myocardial infarction, digitalis toxicity, A–V block and a host of other clinical circumstances. Fusion forms are frequently seen. However, the QRS complexes are 0.12 second or wider and display a bizarre configuration. Beats originating in the left ventricle, more peripherally than the fascicles, produce slurred, monophasic R waves in lead V_1. The patterns of rSr′ or rSR′ are not seen. His bundle electrography contributes to the diagnosis by showing no His spikes before the escape QRS. The His spikes are usually buried within the ventricular complex. Only infrequently are retrograde His spikes, and even more rarely, retrograde P waves found after the ventricular potentials. However, the absence of a His spike before or after a QRS complex may simply reflect movement of the catheter away from the His bundle for that beat. This is a common occurrence when the magnitude of atrial and ventricular contractions change from beat to beat because of a changing P–R relation.

Classic junctional escape beats without aberrancy: These arise from the main His bundle and are identical in QRS configuration with conducted sinus beats (Case 7, Fig. 10). The important diagnostic feature is that His–Q intervals are identical for escape and sinus beats (Table II). Aberrancy, when present, is seen only in early junctional or capture beats but not in escape beats.[15]

Junctional escape rhythm with preexisting aberrancy: Here, the previous tracings taken before the onset of the junctional rhythm show the aberrancy to have been present in conducted beats. As shown in Figure 11 (Case 8), an incomplete right bundle branch block unaccompanied by axis shift was present in junctional beats recorded in September 1970, as well as in 2 previous electrocardiograms taken in 1967 and 1968. The relation between the P wave and the QRS complex suggests an origin near and above the A–V node for 1967, below the A–V node for 1968 and below the A–V node with retrograde V–A block for the 1970 tracing. The His–Q intervals are the same in escape beats 1, 2 and 4 as for the conducted beat 3; therefore, both impulses travel the same path and the aberrancy is present because of the already existing conduction impairment in the right bundle branch.

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The Preoperative and Operative Assessment of Aortic Regurgitation

Cineaortography vs. Electromagnetic Flowmeter

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Supravalvular cineaortography, the most commonly employed procedure for the assessment of aortic regurgitation, is a semiquantitative technique. The surgeon's estimation of aortic regurgitation present at surgery may differ appreciably from the cineaortographic prediction. To evaluate the aortographic technique, a sine wave electromagnetic flowmeter was applied to the ascending aorta of 25 patients who underwent thoracotomy after cineaortography had demonstrated aortic regurgitation graded 1+ to 4+ by conventional grading criteria. The percent of retrograde to forward aortic flow and the mean volume regurgitation (ml/diastole) was compared with the cineaortographic grade. In 5 patients with a cineaortographic grade of 1+, aortic retrograde flow ranged from 5 to 17 percent of forward flow and mean volume regurgitation from 3 to 13 ml/diastole. Seven patients with a cineaortographic grade of 2+ had retrograde flow ranging from 8 to 75 percent with volume regurgitation ranging from 6 to 60 ml/diastole. In 12 patients with 3+ regurgitation, the retrograde flow varied from 17 to 86 percent of forward flow with a volume regurgitant range of 6 to 121 ml. The single patient with grade 4+ aortic regurgitation had a retrograde flow of 49 percent and a mean volume regurgitation of 31 ml.

The severity of aortic regurgitation estimated by cineaortography may differ greatly from that determined by quantitative flow measurement at the time of thoracotomy.

Massive aortic regurgitation, in the absence of extreme left ventricular failure, can be detected readily by bedside clinical examination. However, it has long been recognized that the character of the diastolic murmur, the level of the systemic diastolic pressure, the amplitude of the arterial pulse pressure and other signs of aortic valve disease do not permit the assessment of moderate to moderately severe regurgitation with the precision needed for preoperative evaluation.[1–5] An accurate estimation of the magnitude of aortic regurgitation in a patient with valvular disease is needed not only to determine if aortic valve replacement should be undertaken, but also to predict if reflux of blood through the aortic valve will increase the technical problems and risk of open mitral valve surgery. Significant aortic regurgitation during cardiopulmonary bypass may appreciably decrease coronary perfusion pressure and also obscure the operative field during operation on the mitral valve.

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TABLE I

Preoperative and Operative Findings in 25 Cases

Case no.	Diagnosis	Catheterization				Operation					
		Cine-aorto-graphic Grade of AR	Net Forward Flow (liters/min)	Blood Pressure (mm Hg)	Ventricular Rate (beats/min)	Forward Stroke Volume (ml)	Diastolic Regurgita-tion (ml)	Percent Regurgi-tant to Forward Flow	Net Forward Flow (liters/min)	Blood Pressure (mm Hg)	Ventricular Rate (beats/min)
1	AR	3	4.03	115/60	108	47	21	45	2.64	100/80	103
2	AR	3	5.33	145/40	135	51	21	41	3.64	140/85	121
3	AR	3	7.5	120/40	78	...	...	34	...	160/70	68
4	AR	3	...	125/75	112	60	20	34	3.56	120/60	90
5	AR	3	5.7	125/57	65	87	42	48	4.89	120/60	110
6	AR,AS	2	7.7	127/50	84	103	43	42	4.24	146/80	71
7	AR,AS	3	3.96	120/80	86	...	...	86	...	120/70	87
8	AR,AS	1	2.24	130/75	75	28	3	10	1.71	90/50	68
9	AR,AS	1	6.9	100/60	75	63	6	9	3.67	90/80	64
10	AR,AS	3	4.4	105/50	92	130	56	43	4.81	90/35	65
11	AR,AS	1	4.56	102/60	86	70	12	17	4.42	115/60	76
12	AR,MS	1	4.36	125/65	78	47	3	5	3.57	90/65	80
13	AR,MS	1	...	85/55	78	38	5	14	2.84	50/35	87
14	AR,MI	3	...	120/55	87	110	86	78	1.98	120/60	82
15	AR,MI	3	3.5	90/52	80	98	54	57	3.29	105/60	78
16	AR,MI	3	2.58	117/43	87	145	57	39	7.96	125/25	90
17	AR,MI	2	3.04	138/56	74	78	58	75	1.64	90/40	84
18	AR,AS,MS	4	...	130/55	88	62	31	49	2.75	100/70	87
19	AR,AS,MS	2	4.0	120/60	87	133	11	8	9.54	157/67	78
20	AR,AS,MS	3	3.95	120/60	61	93	61	65	2.21	100/60	68
21	AR,AS,MS	2	5.5	95/50	60	113	12	11	8.45	85/55	84
22	AR,MI,MS	2	3.9	140/70	75	55	6	11	3.48	130/80	71
23	AR,AS,MI,MS	3	...	145/70	87	38	6	17	2.71	90/50	86
24	AR,AS,MI,MS	2	3.55	108/50	75	100	60	60	3.68	110/50	92
25	AR,AS,MI,MS	2	3.23	170/75	64	40	8	20	3.20	110/70	100

AR = aortic regurgitation; AS = aortic stenosis; MI = mitral insufficiency; MS = mitral stenosis.

Several sophisticated and, in some cases, rather cumbersome methods have been described for the determination of the severity of aortic regurgitation induced in experimental animals or existing as a result of disease in human patients. These methods have included the use of indicator-dilution curves,[6–9] volume quantitative angiography[10] and intravascular electromagnetic flowmeter recordings of forward and retrograde aortic flow.[11] However, supravalvular cineaortography remains the most commonly employed clinical technique for the preoperative assessment of the severity of aortic regurgitation.[1,2,4,5,12–16] This method requires a visual estimation of the volume of opacified blood regurgitating into the left ventricle, and is considered only a semiquantitative technique.[10,11,14] During several years' experience with supravalvular cineaortography, we have found, as have others,[5,15] that the surgeon's impression of the magnitude of aortic regurgitation found at operation may differ appreciably from the severity of regurgitation predicted by the cineaortogram. The surgeon's estimation of the severity of regurgitation found during cardiopulmonary bypass has generally been based upon a visual impression of the amount of blood refluxing into the ventricle, or by the very gross measurement of the suction flow required to insure a dry field.[3,5]

The development of reliable electromagnetic flowmeters[17] permits the accurate assessment of forward and retrograde aortic flow when the flowmeter probe can be applied to the ascending aorta at the time of thoracotomy. This method has been employed to determine the volume of regurgitation present at surgery, and to observe changes in flow that occur after aortic valve replacement.[18–20] Delin et al.[20] studied 4 patients with aortic regurgitation. They found that 2 with "moderate" aortic insufficiency determined by aortography had a retrograde aortic flow of 42 to 50 percent of forward flow. Their 2 patients considered to have severe aortic regurgitation by aortographic criteria had a measured retrograde flow of 64 to 69 percent of forward flow. Others who have employed the flowmeter technique for the measurement of aortic regurgitant flow at thoracotomy did not undertake a comparison of the measured regurgitation with the aortographic grading. Therefore, the present

study was undertaken to apply the objective quantitation possible with the electromagnetic flowmeter to evaluate the accuracy of supravalvular cineaortography and to determine if the surgeon's impression of occasional unreliability of aortography is valid.

Methods

In 25 adult patients with aortic regurgitation, left heart catheterization and cineaortography were performed with subsequent electromagnetic flowmeter measurements of phasic aortic blood flow recorded during thoracotomy. Five patients had isolated aortic insufficiency without evidence of other valvular disease. The remaining subjects had other associated valvular lesions (Table I). Retrograde aortic and left ventricular catheterization was accomplished in all patients by the percutaneous femoral arterial technique after premedication with meperidine. Supravalvular aortography was performed with injection of 45 to 50 ml of contrast medium at a pressure of 35 kg/cm^2. Ventricular and aortic pressures were measured using Statham P23Db transducers. Cardiac output determinations were obtained for 20 patients by the indicator-dilution method using indocyanine green dye.

The cineaortograms were reviewed by 2 observers who had not participated in the catheterization study. The severity of aortic regurgitation, estimated from the cineaortograms, was graded on a scale of 1+ to 4+ according to the criteria of Cohn et al.[5] This method of grading, which differs in no significant detail from that reported earlier from other laboratories,[1–13] follows:

1+—a small reflux of contrast material into the left ventricle during each diastole with complete clearing during the subsequent systole.

2+—faint, but incomplete, opacification of the left ventricle during diastole with the contrast material not being cleared with each systole.

3+—progressive opacification of the left ventricle during several cardiac cycles with ultimate complete opacification.

4+—complete opacification of the left ventricle with contrast material at the end of the first diastole following injection. The ventricle remains completely opacified for several cardiac cycles.

Electromagnetic flowmeter recordings of phasic aortic flow were obtained from the 25 patients at subsequent thoracotomy. Halothane-nitrous oxide-oxygen anesthesia was employed in 22 patients. Morphine sulfate-nitrous oxide-oxygen anesthesia was used in the remaining 3. After thoracotomy, the ascending aorta was exposed, and a Statham flow transducer of the cuff type with an interval diameter of 26/mm or 32/mm was placed around the ascending aorta 5 to 7 cm above the base of the heart. Patients were excluded from this study if the circumference of the ascending aorta was too small for a snug fit by the smaller probe or too large to permit uncompromised aortic flow when the larger probe was used. The flow probes were energized with a Statham M-4,000 sine wave electromagnetic flowmeter, and curves of phasic flow were recorded simultaneously with an electrocardiogram and radial arterial pressure pulse. All phasic flow recordings were obtained before institution of cardiopulmonary bypass. Zero flow was established by cross-clamping the aorta as close to the heart as possible. Cross-clamping of the aorta was accomplished in 17 patients before the heart had been cannulated for cardiopulmonary bypass; in the 8 others, cardiopulmonary bypass was initiated before recording the zero flow base line. Care was taken to isolate the flow probe from any metal instrument that might distort the electromagnetic field.

Determination of forward and retrograde volume flow: The flow probes were calibrated for absolute volume flow with isotonic saline solution in a closed-loop system designed in our laboratory. This system is quite similar to that outlined by Case et al.[21] The response to both forward and reverse flow was linear and the calibration curves were reproducible, showing good agreement with the calibrations supplied by the probe manufacturer.

Since the electromagnetic flow curves represent flow velocity versus time, volumetric flow was determined by integrating the areas under the flow curve. Forward flow was determined from the area of the curve above the base line and retrograde flow from the area of the flow pattern below the base line. At least 10 consecutive cardiac cycles were measured for each patient, and the mean value of volume flow/beat was determined. The ratio of regurgitant to forward volume flow was multiplied by 100 to obtain percent regurgitation. Total forward flow (liters/min) was obtained by multiplying the total forward stroke volume by the pulse rate. Total regurgitant flow was similarly determined from the regurgitant stroke volume. Net forward flow (liters/min) was determined as the difference between the total forward flow per minute and total regurgitant flow per minute.

Results

The results of the preoperative and operative studies obtained from the 25 patients in this series are summarized in Table I. The cineaortographic grade of aortic regurgitation ranged from 1+ to 4+, and the electromagnetic flowmeter determination of the percent regurgitant flow ranged from 5 to 86 percent. The electromagnetic flowmeter recording from 1 patient with moderately severe aortic regurgitation is shown in Figure 1. This subject (Patient 24, Table I) had a total forward stroke volume of 100 ml/systole. The retrograde diastolic flow volume was 60 ml/cardiac cycle. Therefore, the retrograde flow represented 60 percent of total forward flow. For comparison, Figure 2 illustrates the phasic aortic flow pattern in a patient with a normal aortic valve. The small negative deflection in early diastole apparently reflects normal early diastolic flow. This normal pattern is the same as that recorded by others from subjects with normal aortic valves or properly functioning aortic prostheses.[18–20]

Percent regurgitation estimated by electromagnetic flowmeter: In Figure 3, the preoperative cineaortographic grade of aortic regurgitation is plotted against the percent regurgitation mea-

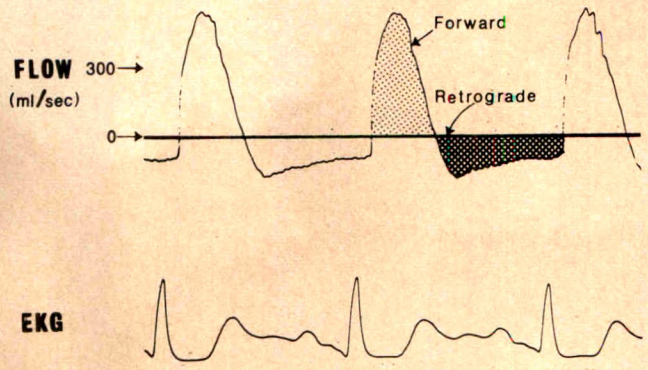

Figure 1. Flowmeter recording of phasic aortic flow of patient with moderately severe aortic regurgitation. Forward stroke volume (**light stippled area** above the base line) was measured as 100 ml/systole. Retrograde flow (**dark stippled area** below the base line) was 60 ml/diastole. Thus, retrograde flow was, 60 percent of forward flow.

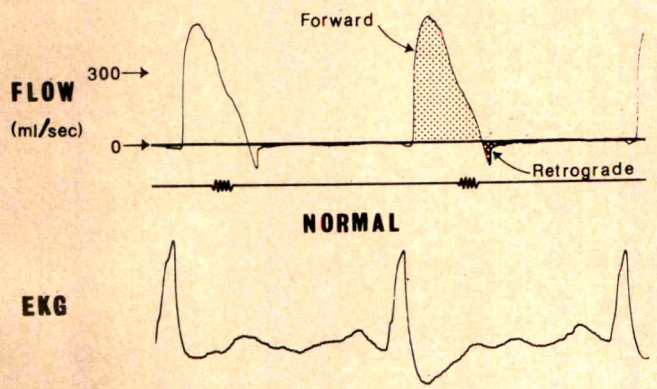

Figure 2. Electromagnetic flowmeter pattern from a patient with a normal aortic valve. The small negative deflection in early diastole reflects normal, early diastolic flow with aortic valve closure.

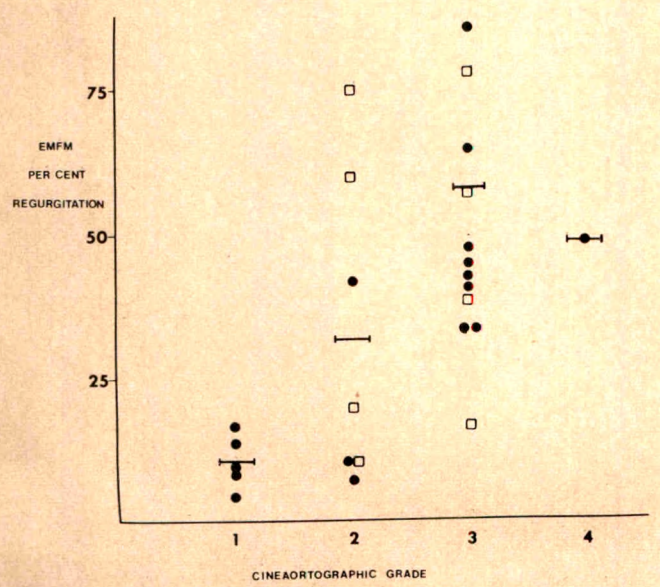

Figure 3. Electromagnetic flowmeter (EMFM) determination of percent regurgitation at operation is plotted against the preoperative cineaortographic grade of aortic regurgitation for the 25 patients in this study. Persons with co-existing mitral insufficiency are designated by squares.

sured by the electromagnetic flowmeter in each of the 25 patients in this study. Eight patients are represented by squares rather than circles. These patients had mitral insufficiency in addition to aortic regurgitation. Since the cineaortographic grading depended in part upon the amount of contrast material remaining in the ventricle after each systole, it seemed appropriate to designate those patients with mitral regurgitation to determine if escape of dye into the left atrium might influence the grading of aortic disease. The horizontal bar in each cineaortographic grade represents the mean percent regurgitation for that grade. Patients with an aortographic grade of 1+ had a regurgitant flow ranging from 5 to 17 percent of forward flow. Those with an aortographic grade of 2+ had a measured regurgitation of 18 to 75 percent and those with a grade of 3+ had a range of 17 to 86 percent. Although the mean value for the percent regurgitation increased for each successive cineaortographic grade between 1 and 3, a wide overlap is apparent. For example, 4 of the 19 patients considered to have 2+ or 3+ regurgitation by the aortographic method had a percent regurgitation within the range found for patients with a cineaortographic grade of 1+. Two of the patients with an aortographic grade of 2+ had a percent regurgitation higher than the mean for grade 3+, and the single patient considered to have 4+ regurgitation had a regurgitant percentage essentially the same as the mean for the 2+ grade. The presence of mitral insufficiency did not seem to result in a consistent underestimation of aortic regurgitation.

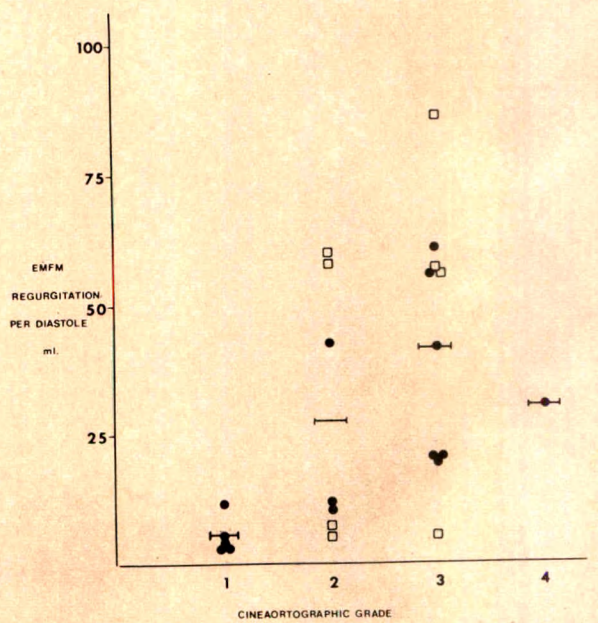

Figure 4. The electromagnetic flowmeter (EMFM) determination of volume of regurgitation (ml/diastole) is plotted for 23 patients against the preoperative cineaortographic grade. Patients with coexisting mitral regurgitation are designated by squares.

Absolute volume of regurgitant flow: Since the visual grading of the cineaortogram depends upon opacification of the ventricle, the grading might be considered more reasonably influenced by the absolute volume of regurgitant flow than by the percentage of forward flow refluxed into the ventricle. In Figure 4, the cineaortographic grade of regurgitation is plotted against the electromagnetic flowmeter determination of absolute volume of regurgitant flow (ml/diastole). Twenty-three points are presented on this graph, since the electromagnetic flowmeter results from 2 patients could not be used to calculate absolute volume of regurgitation. Difficulty with the recorder during the study of these 2 patients made it necessary to employ a linear but noncalibrated channel. An accurate determination of the percent of regurgitant flow could be made by comparison of the curves of forward and retrograde flow, but absolute volume quantitation could not be expressed accurately.

Regurgitant flow per diastole: When the measured regurgitation is expressed as ml/diastole, there remains a wide overlap among patients with grades 1+, 2+ and 3+ although the mean regurgitant flow increases for each grade. Patients with a grade of 1+ had 3 to 13 ml of regurgitation/diastole and those with a 2+ grade had from 6 to 60 ml of regurgitation/diastole. Patients with an aortographic grade of 3+ had a regurgitant diastolic flow ranging from as low as 16 ml to as high as 86 ml. The single subject with grade 4+ aortic regurgitation had a measured regurgitation of 31 ml/diastole. Mitral insufficiency apparently did not result in consistent underestimation or overestimation of the volume of aortic regurgitation.

Correlation with clinical signs of aortic regurgitation: Although the principal objective of this study was the assessment of the cineaortographic method, the protocol permitted us to compare clinical methods of assessment with the results obtained with supravalvular aortography and quantitative flow measurements. The level of the systemic diastolic pressure, the amplitude of the pulse pressure and the intensity of the aortic regurgitant murmur were compared with the catheterization and operative findings. When the diastolic blood pressure was correlated with the aortographic grade of aortic regurgitation, marked overlap was found in all grades. Patients with an aortographic grade of 1+ or 2+ had diastolic pressures ranging from 50 to 75 mm Hg. Those with an aortographic grade of 3+ or 4+ had diastolic pressures ranging from 40 to 80 mm Hg. A similar overlap was apparent when the diastolic pressure was related to the percent regurgitant flow determined with the electromagnetic flowmeter. The 10 patients with less than 20 percent regurgitation had diastolic pressures ranging from 50 to 75 mm Hg, whereas the 15 patients with greater than 34 percent regurgitation had diastolic pressures ranging from 40 to 80 mm Hg. The diastolic pressure agreed with the aortographic and flowmeter findings in some patients, agreed with neither in some patients, and agreed with one or the other in other patients.

When the amplitude of the arterial pulse pressure was compared with the aortographic and flowmeter results, an overlap similar to that obtained with the diastolic pressure correlation became apparent. Patients with an aortographic grade of 1+ or 2+ had a pulse pressure ranging from 30 to 95 mm Hg, and those with 3+ to 4+ regurgitation had a pulse pressure ranging from 40 to 105 mm Hg. Persons with flowmeter recordings showing less than 20 percent regurgitation had pulse pressures ranging from 30 to 87 mm Hg, and those with greater than 34 percent regurgitation had pulse pressures ranging from 55 to 105 mm Hg. Although patients having major regurgitation demonstrated by aortography or flowmeter records had a mean pulse pressure higher than the mean of the group with less severe regurgitation, the overlap was so great that the predictive value of the pulse pressure was not apparent when considering individual patients. Since the diastolic pressure and the pulse pressure recordings were obtained in the catheterization laboratory, one might anticipate that these methods of clinical examination would correlate more precisely with the aortographic studies than with the intraoperative flow studies. This did not prove to be the case. Both the diastolic pressure and the amplitude of the pulse pressure correlated equally well, and equally poorly, with the results obtained by aortography and electromagnetic flow measurement.

Intensity of the diastolic murmur, in general, showed some rough correlation with the aortographic and flowmeter assessments. However, this agreement was not uniform. The 5 patients with an aortographic grade of 1+ had a murmur of grade 1/6 or 2/6 intensity, but 3 of those with moderate to severe aortographic grades had murmurs of 1/6 or 2/6 intensity. Six patients with grade 2+ aortograms had a murmur of 3/6 intensity, whereas the single patient with a 4+ regurgitation had a murmur with an intensity of 2/6. With the exception of 1 patient with a 2/6 murmur, all subjects with an electromagnetic flow recording indicating greater than 34 percent regurgitant flow had a murmur of 3 to 5/6 intensity. However, 3 of 10 patients with a regurgitant flow of less than 20 percent had a murmur with an intensity of 3/6. These findings agree with the early reports,[1–5] thus indicating that the clinical assessment of the magnitude of aortic regurgitation may vary from the results obtained by other methods of study.

Discussion

The results of this study, consistent with other reports, indicate that supravalvular aortography

can give a reasonable prediction of the amount of aortic regurgitation to be expected at the time of surgery in many patients. The 5 patients in this study with a cineaortographic grade of 1+ had a regurgitant to forward flow of 17 percent or less. However, in many cases, there was poor agreement between the preoperative assessment and the measured regurgitation at operation. For example, 1 patient with an aortographic grade of 3+ had a measured regurgitation 17 percent of total forward flow, whereas 1 with an aortographic grade of 2+ had a regurgitant flow of 75 percent. Lehman et al.[14] in their early report on aortography noted that the procedure gave only a rough estimation of the degree of insufficiency of the aortic valve. Sellers et al.[15] found that results of the angiographic method generally agreed well with the operative findings, but they reported that aortic insufficiency which had been considered minor by aortographic grading was occasionally found to be severe in persons undergoing subsequent surgery for mitral stenosis. Although Cohn and co-workers[5] found that cineaortography was more reliable than the usual clinical method for the preoperative assessment of aortic regurgitation, they noted a marked discrepancy between the aortographic determination and the operative findings in some patients.

Previous assessments of the amount of aortic reflux present at surgery have been imprecise and based upon the visual impression of retrograde blood flow from the aorta, or the gross measurement of the suction flow required to maintain a clear operative field during mitral valve surgery.[3,5,22] Suction return under these circumstances, of course, includes not only aortic reflux but coronary and bronchial collateral flow return. The studies of Cohn et al.[5] involved only patients having mitral valve surgery, and the assessment of aortic regurgitation was undertaken during cardiopulmonary bypass, when normal systolic-diastolic time intervals are destroyed. The circumstances in which their study was undertaken might thus have contributed in part to the discrepancy observed in some patients between the preoperative and operative findings. However, in our studies, flow measurements were obtained prior to cardiopulmonary bypass. Therefore, a nearly normal systolic to diastolic flow time existed. The measurement of retrograde to forward phasic aortic flow with the flowmeter permitted accurate quantitation of volume flow through the aortic valve, thus eliminating any error in measurements which might result from the technique of assessing aortic flow by left ventricular suction methods which include coronary and bronchial return.

Explanations for lack of agreement between preoperative and operative findings: If one assumes the well known accuracy of electromagnetic flowmeter measurement when properly applied, 2 possible explanations for the lack of agreement between the preoperative and operative findings are apparent. First, the cineaortograms were recorded under conditions existing in the catheterization laboratory, whereas the flowmeter recordings were obtained under anesthesia during thoracotomy. The heart rate, systolic and diastolic blood pressures and forward flow were determined for each patient during catheterization and compared with these values measured at the time of surgery to define how these variables might influence aortic regurgitation. As noted in Table I, the forward flow measurement tended to be lower in most patients at the time of surgery than that obtained during catheterization. However, in 6 patients the measured forward flow at catheterization and at surgery were essentially the same. In an occasional patient, the output at operation exceeded the output measured at the time of aortography. The heart rate and blood pressure at operation increased or decreased from the catheterization values with relatively equal frequency. We found it impossible to demonstrate any consistent effect of a difference in the heart rate, blood pressure or cardiac output between the time of cineaortography and surgery which might influence the degree of aortic regurgitation. Brawley and Morrow[23] employed electromagnetic flowmeter measurements of phasic aortic flow at the time of surgery to determine the effect of alterations in heart rate, ventricular preload or afterload and catecholamine stimulation upon the amount of regurgitation. They found that an increase in heart rate which could be produced by pacing decreased the systolic ejection rate, whereas regurgitant flow rates remained relatively constant, resulting in constancy of the percent regurgitation. Administration of isoproterenol produced an increase in forward flow and a reduced percent regurgitation, but the percent regurgitation did not change if the heart rate remained constant. Thus, it is not surprising that we were unable to define any variable between catheterization and surgery which might explain the discrepancy observed in some patients between the preoperative and operative assessment of aortic regurgitant flow.

The second possible reason for the discrepancy between the preoperative and operative evaluation is that the cineaortographic method might have inherent errors. The angiographic interpretation might be influenced by the rate of delivery of dye, the position of the catheter above the valve, the size of the aortic mixing chamber, the size of the ventricular mixing chamber and the competence of the ventricle in emptying itself of the dye. All of these possible variables are compounded by the observer factor essential in interpretation of this visual indicator-dilution technique. Since the cineaortographic grade of aortic regurgitation depends on the rate and degree of left ventricular opacification, mitral insufficiency might influence the grade by allowing contrast material to "leak"

into the left atrium. If this were true, the measured aortic regurgitation at surgery might exceed that anticipated from the angiogram. However, the 8 patients in our study with mitral insufficiency did not have a percent of regurgitant flow consistently above the mean regurgitant flow for their respective grades of aortic regurgitation.

Clinical implications: Confidence in the preoperative assessment of aortic regurgitation is not only important to determine if aortic surgery is required but to predict if aortic reflux will compromise the approach for mitral valve surgery undertaken under cardiopulmonary bypass. When an unexpected degree of aortic reflux is present, the operative field may be obscured during mitral valve surgery, whereas aortic reflux results in a decrease in the perfusion pressure to the coronary vessels, kidneys and brain.[3,5,12,22] The understandable concern of a surgeon confronted with a degree of regurgitation not predicted before operation might result in some tendency to exaggerate the unreliability of the aortographic technique. However, the objective quantitation of aortic regurgitation which we have obtained with the flowmeter studies supports the contention that poor correlation between the aortographic prediction and the operative findings is not infrequent. A more reliable method than supravalvular cineaortography is required for the accurate preoperative assessment of the hemodynamic severity of aortic regurgitation.

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The Subendocardial Lymphatics of the Canine Heart

A Possible Role of the Lymphatics in the Genesis of Conduction Disturbances and Arrhythmias

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The subendocardial lymphatics of the canine right ventricle were visualized, and their anatomic relation to the right ventricular conduction system was observed. The lymphatics traversed the main right bundle at many levels and intersected with longitudinal lymphatics following the course of the bundle. In addition, lymphatics crossed the various peripheral branches of the right bundle. The lymphatics anterior to the right bundle tended to be more transversely oriented, whereas those posterior to the bundle were longitudinal, extending from the inferior region to the superior portion of the septum.

It is suggested that the lymphatics may play a role in pathologic lesions involving the conduction system, either by direct involvement, or indirectly, by carrying large concentration of potassium from remote damaged areas. The effect of the potassium could be manifested as a conduction defect due to decreased conduction velocity (for example, A–V conduction defects with inferior infarction or right bundle branch block with anteroseptal infarction) or the development of arrhythmias.

Within recent years there has been increased interest in the numerous conduction defects observed in clinical electrocardiography.[1] Experimental studies have demonstrated the location of the peripheral conduction system by gross staining in man and in the dog,[2–4] and the effect of interruption of its various components on the electrocardiogram.[5–7] The electrocardiogram that demonstrates a conduction defect may give some insight into localization of disease; however, the appearance of a conduction defect on the electrocardiogram does not reveal the nature of the underlying pathologic process. Indeed, there is a controversy as to whether certain conduction defects may be due directly to arteriosclerosis or to other pathologic causes.[8–11] With this in mind, and an awareness of the possible role of the cardiac lymphatics in other pathologic states[12–14] and experimental conditions,[15,16] an investigation was conducted on the relation of the subendocardial lymphatics to the conduction system of the canine heart.

Methods

Twelve dogs were used in this study which was confined to the right ventricle. Evans blue dye was injected into the subendocardial tissue with a no. 30 needle. In 2 dogs, the right ventricle was opened under

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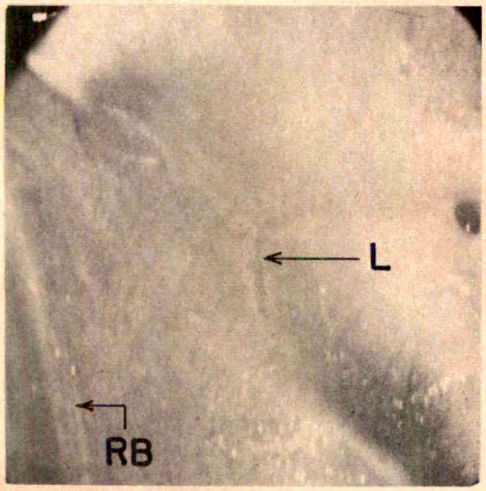

Figure 1. The large unstained, transversely oriented lymphatic (L) is located in the mid right ventricle anterior to the main right bundle (RB) (**white band**), and inferior to the small papillary muscle of the septal leaflets of the tricuspid valve.

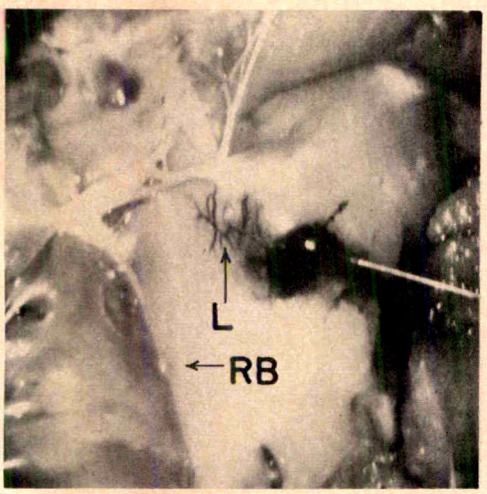

Figure 2. Needle injecting dye in the region of the small papillary muscle of the septal leaflet of the tricuspid valve. Note streaks of lymphatics (L) projecting out of the mass of dye.

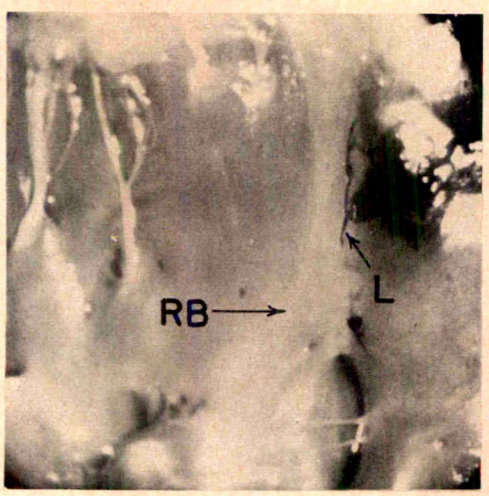

Figure 3. Longitudinal lymphatic (L) of the main right bundle (RB) is filled by way of small transverse lymphatics after injection in the superior portion of the anterior septum.

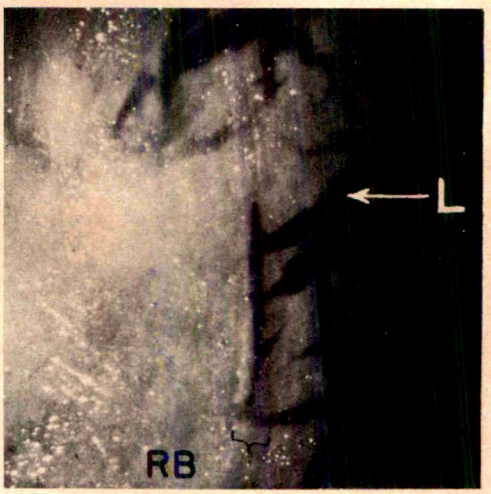

Figure 4. Extrinsic network of lymphatics (L) transversing and extending along the main right bundle (RB).

cardiopulmonary bypass, and several sites around the right bundle were injected. One heart was injected during inflow occlusion. In the remaining animals the heart was removed and washed free of blood, and injected and studied with use of a Zeiss operating microscope and camera. At times it was possible to see a lymphatic channel which could be cannulated directly and injected (Fig. 1). However, in most instances the dye had to be injected into the subendocardial tissue and, when the lymphatics were entered, blue streaks would project out of the mass of injected dye (Fig. 2). The conduction system was identified by gross staining with Lugol's solution, and the relation of the lymphatics to the conduction system was observed.

Results

The subendocardial lymphatics of the canine heart form a vast network of various shapes and formations which may change at different sites. At times they appear more or less singly in a linear fashion; at other times the course is tortuous. The lymphatics may have numerous branches intersecting at nearly right angles, or frequently they may form a loose reticular fishnet-like arrangement intersecting at various angles. A given area may be dense with closely interlacing lymphatics, whereas in other areas lymphatics may be less obvious. The vessels vary in size, with some of the larger trunks actually being visible without stain if one looks closely with the light reflecting at a proper angle. A large prominent lymphatic vessel (approximately 1 mm in diameter) can occasionally be seen under the endocardium in the region between the pulmonary outflow tract and the middle course of the right bundle. This vessel generally traverses several millimeters of the anterior septal region of the right heart chambers somewhat perpendicular to the right bundle (Fig. 1).

There is an anatomic relation between the subendocardial lymphatics and the main right bundle (Fig. 3 to 5). Numerous lymphatics traverse the anterior surface of the right septum and cross the

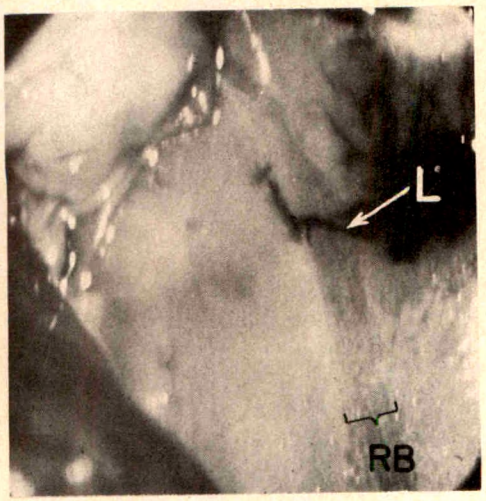

Figure 5. Transverse lymphatic (L) crosses the main right bundle (RB) and becomes superiorly oriented.

right bundle at approximately right angles. They are seen in the middle portion of the right bundle as well as the superior portion near the tricuspid valve and the inferior portion near the base of the anterior papillary muscle. The most striking feature of the relation between the lymphatics and the right bundle is the presence of a generally single longitudinal lymphatic pathway running parallel to the right bundle (Fig. 3 to 5). This channel hugs the right bundle and communicates with the numerous lymphatics that cross the bundle.

Other, generally smaller lymphatic vessels cross the anterior (Fig. 6) and posterior branches (Fig. 7) of the right ventricular conduction system. There are also lymphatics crossing the lateral conduction network covering the right mural wall. The lymphatics that come in contact with the various branches of the conduction system beyond the main right bundle tend to be more sparse and have no specific angular relation to the conduction fibers.

The lymphatics posterior to the right bundle are longitudinally oriented and may extend from the inferior regions of the heart all the way up to the tricuspid valve (Fig. 8 and 9). On the other hand, lymphatics anterior to the right bundle are more transversely oriented, although shorter more or less longitudinal vessels may be seen.

The lymphatics on the papillary muscles were apparent as fine channels near the insertions of the chordae tendineae or on the muscle surface (Fig. 10). Lymphatics could be seen near the base of the small papillary muscle arising from the region near the pulmonary conus as well.

Discussion

The lymphatics are fine thin-walled delicate structures which are frequently obscured in the postmortem state and are generally very difficult to observe.[17] However, informative studies can be

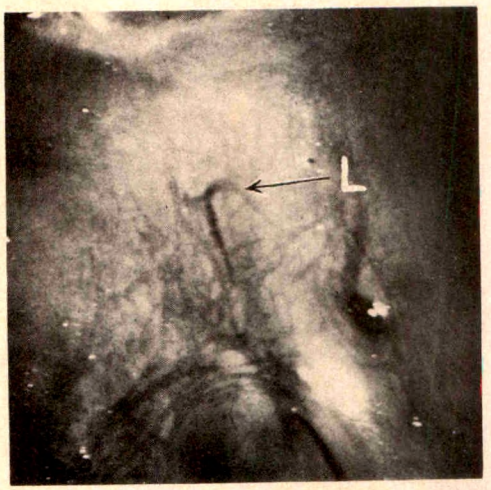

Figure 6. Lymphatic (L) oriented in a semicircular shape amidst the anterior branches of the peripheral right ventricular conduction system.

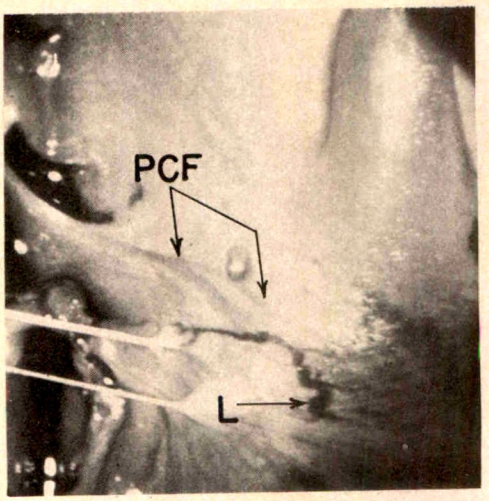

Figure 7. Lymphatics (L) crossing some of the peripheral conduction fibers (PCF) of the posterior branches of the right ventricular conduction system. Because of the anatomic relationship to some of the posterior branches, it is possible that high potassium concentration from remote tissue damage might cause slower conduction velocities in these fibers thereby enhancing the development of reentry.

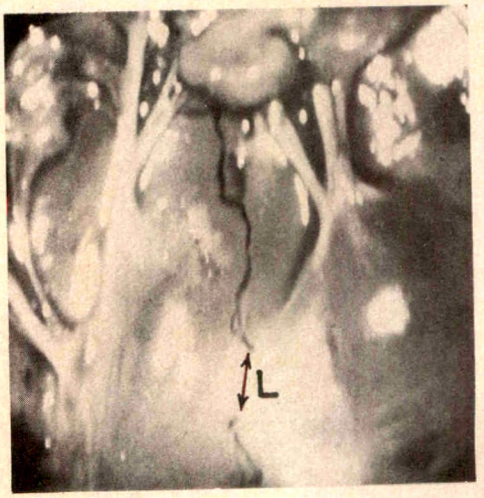

Figure 8. Lymphatic channel (L) extending from the inferior regions of the septum to the septal leaflet of the tricuspid valve.

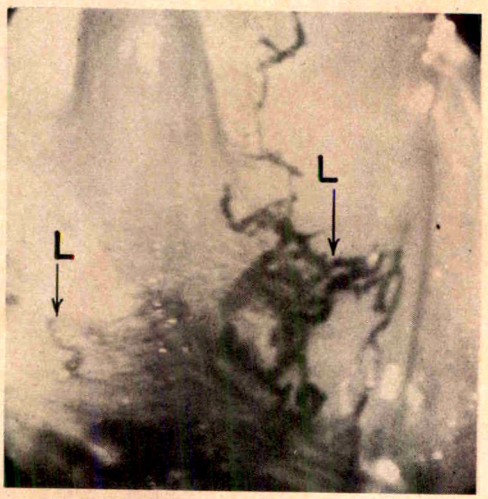

Figure 9. Close-up of the lymphatics (L) extending superiorly from the inferior septal region. It is theorized that such lymphatics could carry high concentrations of substances (for example, potassium) from the site of an inferior infarction superiorly to the regions of the A–V conduction system and cause various A–V conduction defects.

made with the use of special dyes or techniques.[18] Patek[19] described the anatomy of the cardiac lymphatics and demonstrated that the subendocardial lymphatics connect to a myocardial and subsequently to an epicardial plexus leaving the heart by several main drainage trunks. He noted that valves were uncommon in subendocardial plexus.

These studies demonstrate a well defined system of lymphatic vessels beneath the endocardial surface of the right ventricle brought forth by injection of Evans blue dye. The lymphatic vessels exist in various anatomic arrangements (Fig. 11). In general, the lymphatics in the anterior septal

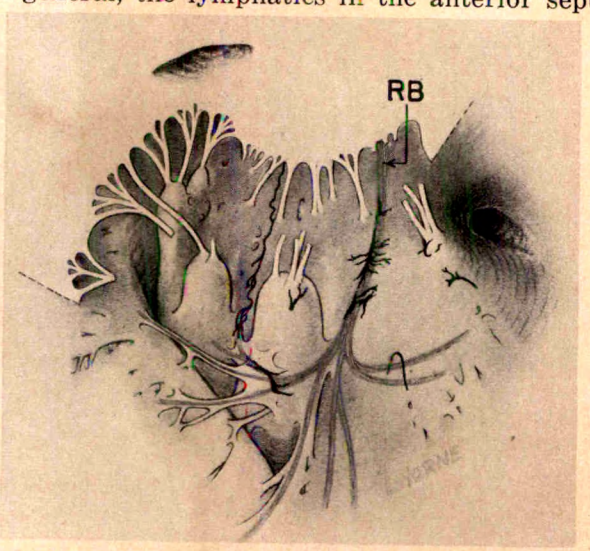

Figure 11. Composite diagram illustrating the relationship of the canine endocardial lymphatics to the right ventricular conduction system. Note the transverse and longitudinal lymphatics of the right bundle (RB) and the lymphatics crossing some of the peripheral conduction fibers. Lymphatics anterior to the bundle appear somewhat more transversely oriented than the longer longitudinal branches posterior to the bundle.

Figure 10. Fine lymphatic channels longitudinally oriented on the posterior septum.

area seem to appear more transversely oriented, whereas lymphatics in the posterior septum appear longitudinal. In regard to the conduction system per se, lymphatics not only traverse the main bundle, but form a longitudinal pathway along the course of the right bundle. The anterior, lateral and posterior branches of the right bundle are also traversed by lymphatics; however, the density of lymphatics seems to be greater in the region of the main right bundle than in the region of the peripheral conduction tissue. Certain lymphatic vessels may at times appear relatively large, in particular, the centrally located lymphatic just anterior to the mid-portion of the main right bundle.

The subendocardial lymphatics are part of an extensive transport system capable of returning interstitial materials to the vascular system. Accordingly, if these fine thin-walled transport vessels could become involved with the pathologic process, it is conceivable that adjacent structures might also be affected. For example, inflammation of the perilymphatic structures might lead to subsequent fibrosis and interruption of normal function (delayed or decremental conduction and block).

There are specific pathologic entities relating to the conduction system such as sclerosis of the cardiac skeleton described by Lev[10] and degenerative changes of the conduction system per se described by Yater et al.[8] and Lenegre.[9] The question is raised whether these entities as well as myopathies, in part, have their effects on the conduction system mediated by the lymphatics of the heart.

Possible role of lymphatics in conduction disturbances: Cardiac lymph reflects myocardial potassium changes.[20] Accordingly, one might anticipate that lymphatics draining areas of tissue damage might carry away waste products such as large concentrations of potassium from injured cells. Such relatively high levels of potassium might in turn equilibrate across the lymphatic wall to the immediate environment of the conduc-

tion tissue; possibly they would alter conduction velocity, producing transient slowing or block such as is frequently observed in certain myocardial infarctions. Hence, the appearance of intermittent conduction defects might be due to tissue damage in a remote area linked to the conduction system by the lymphatic system as well as to direct damage by the pathologic process to the conduction tissue.

The appearance of various degrees of atrioventricular (A–V) block is a frequent transient phenomenon associated with inferior myocardial infarctions. The block is generally thought to be due to occlusive disease in the right coronary artery. However, the block frequently occurs several days after the onset of the inferior infarction, and the terminal branches of the right coronary artery supplying the inferior myocardium are remote from the branches supplying the A–V node. The anatomic study in this paper demonstrates a lymphatic network in the inferior portion of the right heart chambers which drains superiorly to the region of the A–V node (Fig. 8 and 9). Accordingly, it is conceivable that inferior tissue damage would liberate, over a period of time, vast stores of intracellular potassium which would be transported by way of these lymphatics to the region of the A–V node. In so doing, the equilibration of potassium through the lymphatics could alter the extracellular environment of the A–V junction and slow conduction velocity, resulting in a gradual rather than immediate appearance and disappearance of A–V conduction delay after an inferior infarction.

In a similar manner, damage to the tissue of the anterior septum would result in lymph flows toward the right bundle, possibly causing transient complete right bundle branch block. Various peripheral branches of the right ventricular conduction system might also become involved depending on the location of the myocardial damage.

Possible role of lymphatics in arrhythmias: The same conditions might be applicable to the development of reentry wherein lymphatics carrying high potassium concentrations from remote damaged areas bring normal myocardium or some strands of Purkinje fibers in contact with a high potassium environment[21] thereby delaying the passage of the wave front at a given area. If the involved area has unidirectional block characteristics, and the delayed wave front finds it possible to emerge and activate adjacent myocardium which is no longer refractory, ectopic beats will be set up by means of a reentry mechanism.

The effect of local increases in potassium, as determined by the lymphatic pathways, could also bring the resting membrane potential of a given area closer to the threshold of excitability, thereby setting up ectopic foci. On the other hand, delays in conduction velocity of tissue may play a role in the development of exit and protection blocks.

Thus, the recognition of an anatomic relation of the lymph system to the conduction fibers might provide some insight into both permanent and transient block patterns and possibly the induction of some arrhythmias seen in clinical electrocardiography.

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Electrical Properties of the Thoracic Veins

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This preliminary study demonstrates that the conduction velocity in the venae cavae and the stimulation threshold and refractory period of the venae cavae, azygos and pulmonary veins in dogs were very similar to those found in atrial muscle. It is quite likely that atrial muscle extends for a distance into these veins and that the muscle receives vagal innervation. Superior vena caval pacing was performed in 1 patient.

The following preliminary study was designed to investigate some of the electrical properties of the venae cavae, azygos and pulmonary veins in dogs. In addition, superior vena caval pacing was performed in 1 patient.

Methods

Five mongrel dogs weighing between 14 and 20 kg were anesthetized with pentobarbital sodium (30 mg/kg body weight). Under artificial ventilation, the chest was opened in the midline. The pericardium was incised and used to cradle the heart. The superior and inferior venae cavae were dissected free from reflected pericardium and connective tissue for a distance of 3 to 4 cm. Similarly, small portions of a pulmonary vein and the azygos vein were exposed. Bipolar recording electrodes were placed at the angle formed by the superior vena cava and right atrial appendage (SVC–RA junction) and the inferior vena cava and body of the right atrium (IVC–RA junction). All distances were measured directly superiorly or inferiorly with respect to these electrodes along the ventral plane of the venae cavae. Bipolar recording and stimulating electrodes were placed on the right atrium and a recording electrode on the right ventricle. The stimulating electrode was always held perpendicular to the wall of the tested structure; the 2 electrodes of the bipolar stimulating pair were 2 mm apart. The right and left vagus nerves were isolated in the neck and cut, and their distal ends were stimulated with a Grass stimulator. With the use of a small bipolar pronged electrode, we explored the stimulation threshold, refractory period and conduction velocity in the venae cavae, and measured the stimulation threshold and refractory period of the azygos and pulmonary veins. Since pulmonary venous and azygos attachments to the atria were small and frequently difficult to isolate, we made no attempt to map these structures or to measure conduction velocity in them. Stimuli of 2 msec duration were delivered by a Tektronix pulse generator, triggered by a digitally controlled interval generator at an intensity 1.5 times that of the stimulation threshold. The minimal voltage applied to the tested vein, which initiated a propagated atrial response, established the stimulation threshold. During all testing we carefully avoided stimulation of contiguous structures. In 1 dog and 1 patient, a bipolar pacing catheter was introduced into the vena cava and pacing was instituted.

In the open chest animal, surface structures exposed to room air tend to dry and cool. Periodic bathing of the veins and heart with a

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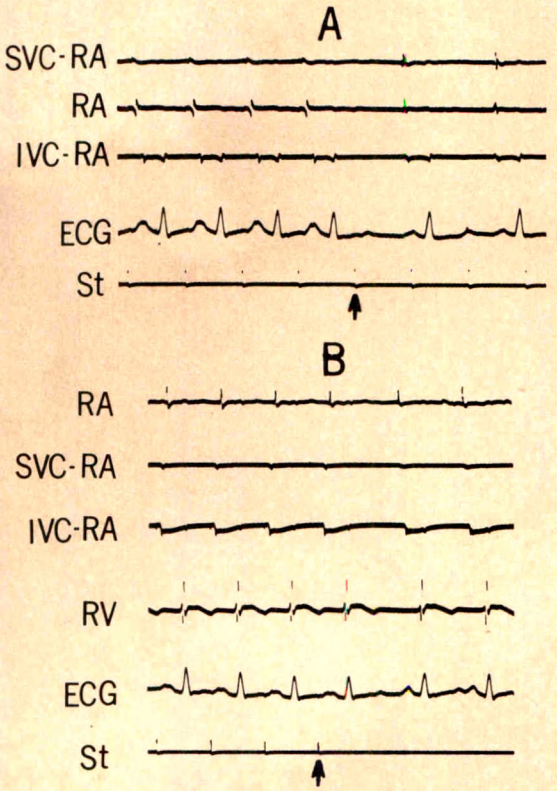

Figure 1. Superior and inferior vena caval pacing. **A,** superior vena caval pacing 20 mm above the SVC–RA junction; **B,** inferior vena caval pacing 5 mm below the IVC–RA junction. The **arrow** indicates cessation of pacing, followed by the escaping sinus rhythm. Stimuli are recorded past the arrow in **A,** although the superior vena cava is not being paced. ECG = lead II of electrocardiogram; IVC–RA = electrogram at inferior vena caval-right atrial junction; RA = right atrial electrogram; RV = right ventricular electrogram; ST = stimulus artefact; SVC–RA = electrogram at superior vena caval-right atrial junction. Paper speed 100 mm/sec. Basic cycle length 230 msec.

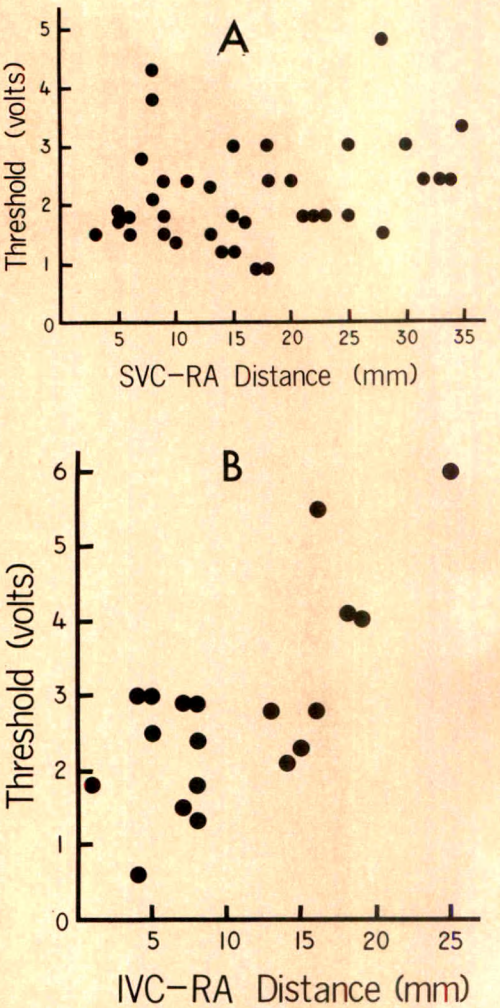

Figure 2. Graph demonstrating the relation between pacing threshold plotted on the ordinate and distance above the SVC–RA junction (**A**), or below the IVC–RA junction (**B**) plotted along the abcissa.

sodium chloride solution at room temperature prevents drying but does not prevent cooling below 37C. This factor may spuriously reduce the calculated conduction velocity to some degree. The latter was determined by dividing the distance measured along a straight line between stimulus applied to the vena cava and response recorded at the caval-atrial junction. The resulting figures were then averaged.

The SVC-RA junction on the ventral surface of the dog is fairly easy to establish grossly, but it is much more difficult to determine the point at which the inferior vena cava joins the right atrium. Straying laterally posterior to the sulcus terminalis encounters the venous portion of the right atrium. Because of this, and the fact that atrial muscle appears to extend for a much shorter distance into the inferior vena cava, data obtained from stimulating the latter structure must be interpreted cautiously.

Results

Mapping: Propagated responses to the atrium could be initiated by stimulation of the superior vena cava up to, on the average, 32 mm above the SVC-RA junction in 4 dogs (Fig. 1A). Because of mechanical difficulties in 1 dog, the exploring electrode could not be moved any further than 22 mm while still maintaining the desired testing plane. Similarly, propagated responses to the atrium could be initiated by stimulating the inferior vena cava up to, on the average, 14 mm below the IVC-RA junction (Fig. 1B). During the course of a separate dog study, we were able to stimulate a persistent *left* superior vena cava for a distance of 22 mm distal to its junction with the right atrium.

Conduction velocity: The average conduction velocity in the superior vena cava determined for 4 dogs was between 0.6 and 0.7 m/sec. For the inferior vena cava, the average conduction velocity in 3 dogs was between 0.4 and 0.55 m/sec. The stimulus strength used to measure conduction velocity was 1.5 times the stimulus threshold at the area tested.

Stimulation threshold: The stimulation threshold of the superior and inferior venae cavae for all experiments is displayed in Figure 2. The lowest

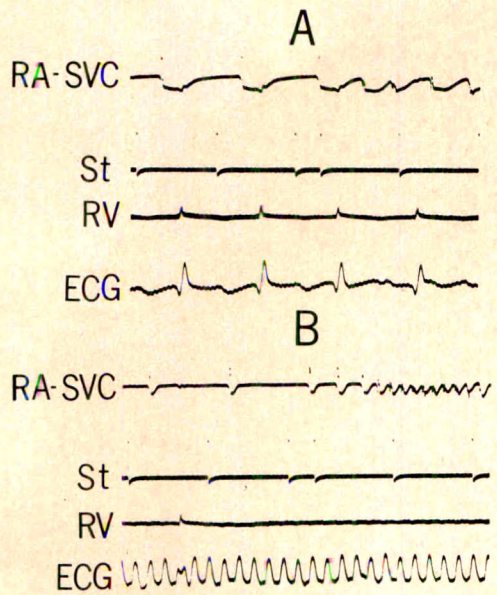

Figure 3. Precipitation of atrial fibrillation by premature left inferior pulmonary vein stimulation. A premature stimulus delivered at a coupling interval of 100 msec initiates a run of premature atrial beats (**A**) and produces sustained atrial fibrillation during vagal stimulation (**B**). Vagal stimulation distorts the inscription of the electrocardiogram in **B** and blocks a number of atrial impulses from reaching the ventricles. Basic cycle length 300 msec. Paper speed 100 mm/sec. Abbreviations as in Figure 1.

values measured were quite comparable to those of the right and left atria in each experiment. High values obtained at greater distances away from the atria may reflect thinning out of cardiac muscle as it terminates and becomes replaced by connective tissue. Precisely accurate stimulation thresholds were difficult to obtain because cardiac movement under the hand-held probe frequently changed the electrode contact. In addition, lateral retraction of the heart to expose the inferior vena cava amplified this problem. Generally, the stimulating probe was held so that a line drawn between the 2 poles was parallel to the border formed by the atrium and the vein.

The average stimulation threshold for the azygos vein in five experiments was 3.0 v, obtained at a distance of 5 to 10 mm from its junction with the right atrium. For the pulmonary vein (generally the left superior) the average stimulation threshold was 2.6 v.

Refractory period: The refractory period of the superior vena cava, established in 4 dogs by determining the shortest interval between 2 caval stimuli which produced a right atrial response, compared closely with the right atrial refractory period at the same cycle length. Immediately after instituting vagal stimulation, the refractory periods of both structures shortened by a similar amount. The refractory periods of the inferior vena cava in 2 dogs and of azygos and pulmonary veins in 1 dog were only slightly longer than comparable superior vena caval or right atrial refractory periods; vagal stimulation similarly promptly shortened the refractory periods of these structures. These observations strongly suggest vagal innervation of the cardiac muscle which extends into the tested venous structures. On at least 1 occasion during testing, premature stimulation of either the venae cavae, the azygos or pulmonary veins initiated atrial fibrillation (Fig. 3). Once begun, atrial fibrillatory impulses also could be recorded in the vena caval and azygos veins (Fig. 4).

Patient Study

A 56 year old white man with coronary artery disease had undergone coronary surgery in the past. During the course of atrial pacing to determine the threshold at which chest pain developed, the superior vena cava was stimulated at various rates up to 120 beats/min with a no. 7 Zucker catheter introduced through the right basilic vein. More rapid pacing was not attempted. The stimulation threshold was 1.5 to 2.0 ma, which was similar to that obtained for the right atrium. Catheter movement precluded consistent pacing at the lower amperage, or accurate determination of stimulation threshold, refractory period or mapping. Chest roentgenogram and electrocardiography established the catheter position to be clearly within the superior vena cava, not the right atrium (Fig. 5). Inferior vena caval pacing using 9 ma was not successful in this patient, although the transvenous catheter method was successful in the dog. A femoral vein approach might allow better catheter positioning to stimulate successfully the inferior vena cava in man.

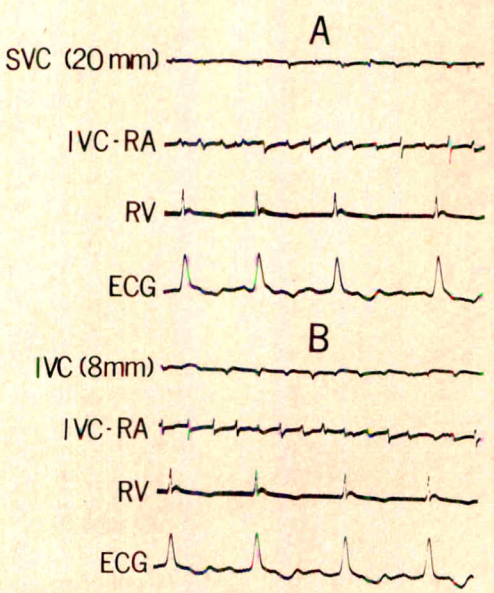

Figure 4. Spontaneous atrial fibrillation, recorded from the superior vena cava 20 mm above the SVC–RA junction (**A**) and from the IVC, 8 mm below the IVC–RA junction (**B**). Paper speed 100 mm/sec. Abbreviations as in Figure 1.

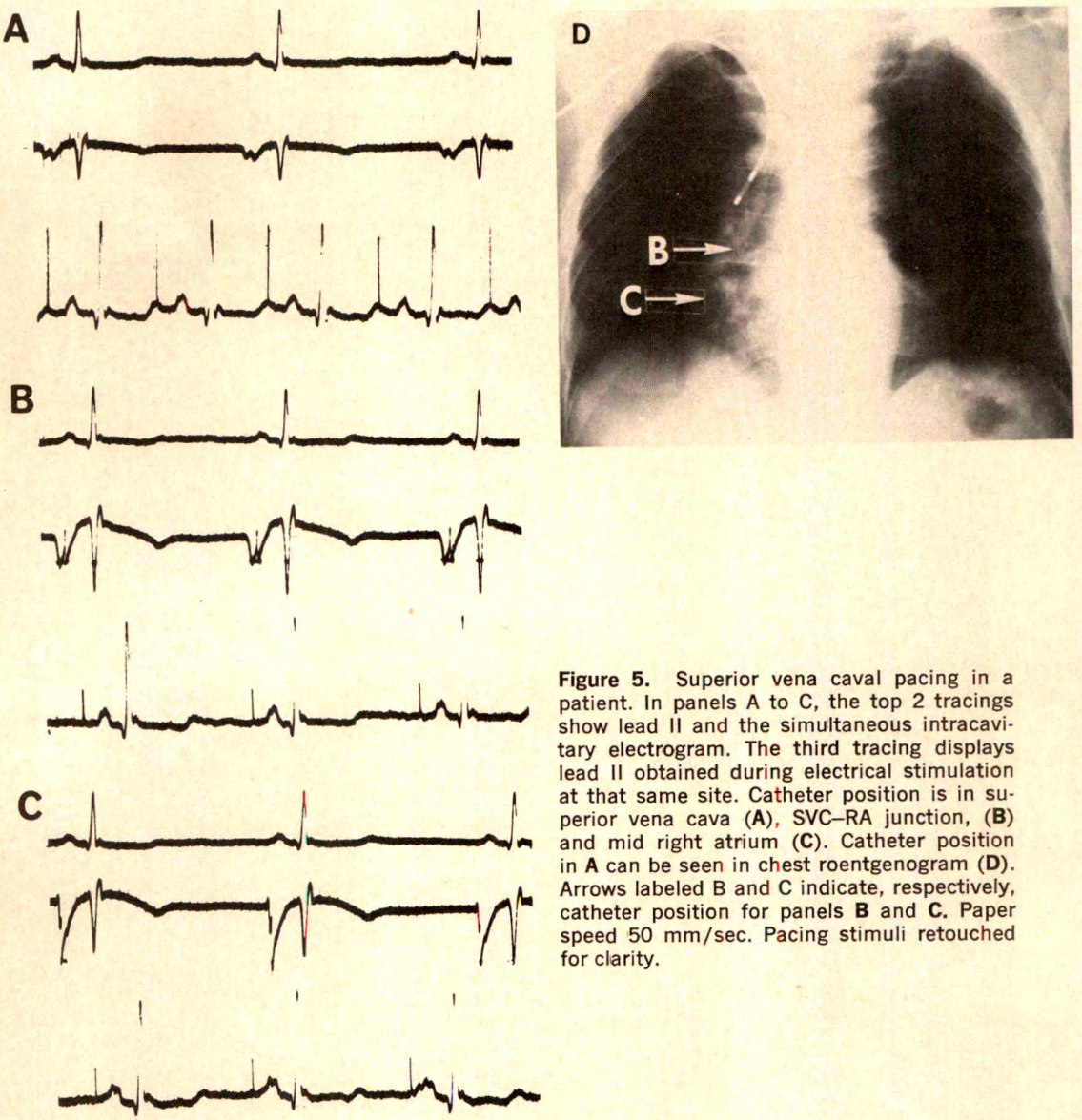

Figure 5. Superior vena caval pacing in a patient. In panels A to C, the top 2 tracings show lead II and the simultaneous intracavitary electrogram. The third tracing displays lead II obtained during electrical stimulation at that same site. Catheter position is in superior vena cava (**A**), SVC–RA junction, (**B**) and mid right atrium (**C**). Catheter position in **A** can be seen in chest roentgenogram (**D**). Arrows labeled B and C indicate, respectively, catheter position for panels **B** and **C**. Paper speed 50 mm/sec. Pacing stimuli retouched for clarity.

Discussion

Brunton and Fayrer[1] first reported spontaneous beating of pulmonary veins and vena cava in 1876, and Lewis et al.[2] described preliminary studies measuring conduction velocity along the atrial border of the venae cavae in the dog in 1914.

Ito and co-workers[3] extensively mapped the spread of activation in the venae cavae of in vitro rabbit preparations, using intracellular recording techniques. Conduction velocity in the superior vena cava was 40 to 80 cm/sec. However, they demonstrated an area of slower conduction (10 to 25 cm/sec) at the proximal junction of both the right and left superior venae cavae with the atrium. Action potentials obtained from this area showed "slight diastolic slow depolarization" and under certain circumstances might initiate arrhythmias. Further, they noted that the inferior vena cava was electrically silent, except near its ostium, and they suggested that different embryological origins of the superior and inferior venae cavae account for their electrophysiologic differences.

Recently, Spach and Barr[4] mapped the spread of atrial excitation in dogs and noted propagation of the wavefront 4 to 5 cm above the SVC-RA junction. They found that conduction velocity near this junction was 0.5 m/sec but increased to 1.3 m/sec in the mid portion of the superior vena cava where the wavefront magnitude also increased. Histologic studies, performed by Jewett[5] of their group, confirmed the presence of cardiac muscle to this level.

Preliminary data in man indicate that the excitation wavefront does not appear to travel as high up the superior vena cava nor to extend to the

azygos vein as it does in dogs. In 1 patient with tetralogy of Fallot and a persistent left superior vena cava, active muscle extended higher in the left than in the right superior vena cava, to a point just below its junction with the left innominate vein.[6]

These data are consistent with our preliminary findings which demonstrate that stimuli delivered to both venae cavae (and in one dog, a persistent left superior vena cava), azygos and pulmonary veins conduct to the atrium with electrical properties very similar to those of the atria themselves. Species differences may account for some of the discrepancies noted.

Clinical implication: The presence of cardiac muscle extending for some distance into these veins may have significant clinical importance. Many clinical situations exist for which long-term atrial pacing may be indicated. To avoid the need for thoracotomy to attach atrial electrodes,[7] Kramer and Moss[8] inserted the catheter into the coronary sinus, whereas Kastor et al.[9] utilized the atrial appendage. (It is possible that successful coronary sinus pacing results, at least in part, from coronary sinus vein stimulation as well as from stimulation of the posterior atrial wall.) Future catheter electrode development may permit fixation of a transvenous pacing catheter in the superior vena cava and avoid entering the heart itself. Since the conclusion of this study, we have been able to perform temporary transvenous superior vena caval pacing in several patients.

Acknowledgment

We thank Gordon K. Moe, MD, PhD, and Carlos Mendez, MD for critical comments.

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Magnesium Sulfate in Digitalis Toxicity

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This study was undertaken to evaluate the mechanism of the antiarrhythmic effect of magnesium sulfate in digitalis toxicity. The egress of potassium from the myocardium after the administration of 1 mg of acetyl strophanthidin into the right atrium was determined in 16 dogs by measurement of the coronary sinus-femoral artery potassium concentration difference. Three infusions of acetyl strophanthidin were given at 2½ hour intervals. Twenty-five percent magnesium sulfate was given simultaneously with the third infusion. Arterial and coronary sinus samples were collected at 2 minute intervals after each infusion.

The mean maximal arteriovenous potassium concentration difference was 0.47 mEq/liter after the first dose of acetyl strophanthidin and 0.80 mEq/liter after the second dose. When magnesium sulfate was given with acetyl strophanthidin, the arteriovenous difference was not significantly different from that of control subjects (0.15 mEq/liter). A high level of magnesium concentration may overcome the acetyl strophanthidin-induced inhibition of transport adenosine triphosphatase. This may explain the efficacy of magnesium sulfate in the treatment of the arrhythmias of digitalis toxicity associated with hypomagnesemia. Although magnesium sulfate blocked myocardial egress of potassium in all studies, arrhythmias still occurred in 60 percent of the animals. This suggests that factors independent of potassium loss from the myocardium underlie the development of some digitoxic arrhythmias.

The antiarrhythmic properties of magnesium sulfate in digitalis-induced arrhythmias have been recognized for many years.[1] We have recently reported that hypomagnesemia facilitates the development of arrhythmias in digitalis toxicity. In hypomagnesemic digitalis toxicity, intravenous administration of magnesium sulfate results in prompt and permanent conversion to sinus rhythm, in contrast to its often transient effect in normomagnesemic digitalis toxicity.[2] The precise mechanisms underlying the antiarrhythmic properties of magnesium sulfate have not been determined.

Digitalis glycosides inhibit the activity of sodium–potassium-dependent membrane adenosine triphosphatase (ATPase), and the action of this enzyme is essential for the maintenance of a normal intracellular potassium concentration.[3,4] The loss of myocardial potassium secondary to inhibition of ATPase is believed to be causally related to the generation of arrhythmias in digitalis toxicity. Adequate magnesium ion is essential for the normal function of membrane ATPase. Not only is magnesium essential for ATPase activity but cellular depletion of potassium has been re-

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TABLE I

Group I: Potassium Concentrations*

	Coronary Sinus	SE	Femoral Artery	SE	Coronary Sinus-Femoral Artery
Control					
1	3.7	0.14	3.7	0.12	0
2	3.8	0.15	3.8	0.14	0
Magnesium sulfate					
2 minutes	3.6	0.16	3.6	0.17	0
4 minutes	3.6	0.18	3.4	0.19	0.2
6 minutes	3.5	0.18	3.5	0.20	0
8 minutes	3.5	0.19	3.5	0.18	0
12 minutes	3.6	0.19	3.5	0.18	0.1
20 minutes	3.5	0.13	3.5	0.14	0

* Mean coronary sinus and femoral arterial potassium concentrations (mEq/liter) ± 1 SEM and the concentration differences after the administration of magnesium sulfate ($MgSO_4$). Average of 8 dogs.

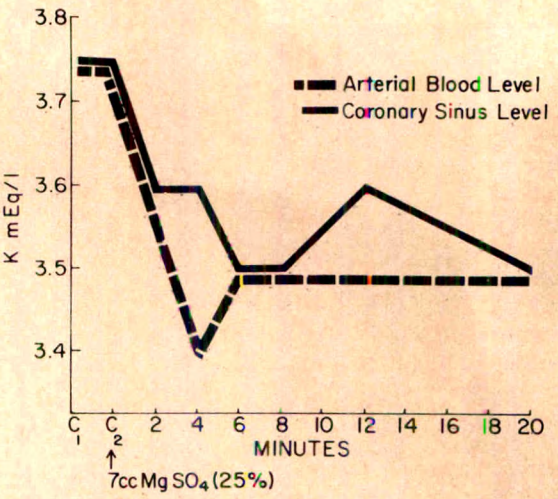

Figure 1. Mean coronary sinus and arterial potassium concentrations after administration of 7 ml 25 percent magnesium sulfate ($MgSO_4$) to 8 dogs.

ported with systemic magnesium deficiency,[5] congestive heart failure,[6] myocardial infarction,[7] and administration of diuretic drugs[8,9] and digitalis.[10]

Observations in our laboratory and in others[11] demonstrated that the intravenous administration of magnesium sulfate alone resulted in a rapid decrease in arterial potassium concentration. We attributed this decrease to a shift of potassium into the cells. We therefore postulated that the antiarrhythmic action of magnesium sulfate might be due to its ability to increase cellular potassium uptake, possibly by enhancing membrane ATPase activity. The purpose of this study was (1) to determine the effect of magnesium sulfate alone on myocardial potassium flux; (2) to determine whether magnesium sulfate would prevent the acetyl strophanthidin-induced myocardial potassium egress; and (3) to correlate the changes in potassium egress from the myocardium with the incidence of toxic arrhythmias.

Methods

All studies were performed in adult mongrel dogs weighing approximately 20 kg. Anesthesia was induced by sodium pentobarbital, 25 mg/kg body weight, administered intravenously, with additional doses administered as necessary to maintain light anesthesia. The dogs were ventilated with 100 percent oxygen through a cuffed endotracheal tube with a Harvard respirator with a tidal volume and rate adjusted to the dog's weight. To facilitate blood sampling, 50 mg of heparin was administered intravenously every 3 hours. Femoral arterial blood pressure was measured by a Statham strain gauge, and monitored on an Electronics for Medicine recorder. Serial lead II electrocardiograms were taken with a direct writing electrocardiograph. The development of atrioventricular dissociation, nodal tachycardia or ventricular tachycardia was taken as evidence of digitalis toxicity. All blood samples were collected in heparinized tubes, centrifuged immediately, and the plasma was separated and frozen. Sodium and potassium were determined by flame photometry using a Beckman DU photometer, and calcium and magnesium by atomic absorption spectroscopy using a Perkin-Elmer Model 214.

Group I: Eight dogs were studied as a closed chest preparation. Coronary sinus and right atrial catheters were placed under fluoroscopic guidance. In addition to the fluoroscopic appearance, the location of the coronary sinus catheter was verified by determining the partial pressure of oxygen simultaneously in several coronary sinus and right atrial samples. After 2 control samples taken 2 minutes apart, 7 ml of 25 percent magnesium sulfate was injected intravenously, and serial samples were obtained simultaneously from the coronary sinus and femoral artery at 2, 4, 6, 8, 12 and 20 minutes. Blood samples were replaced with equal volumes of saline solution. Samples were analyzed for potassium, sodium, magnesium and calcium concentration as noted.

Group II: Six dogs were studied as a closed chest preparation with catheters placed fluoroscopically in the right atrium and coronary sinus. The location of the coronary sinus catheter was verified by the determination of the partial pressure of oxygen, as in Group I. To assure that the effect of acetyl strophanthidin could be duplicated on repeated injections, 0.05 mg/kg of acetyl strophanthidin in 5 ml of saline solution was injected over a 15 second period into the right atrium 3 times at 2½ hour intervals. Seven milliliters of 25 percent magnesium sulfate was administered intravenously simultaneously with the third infusion of acetyl strophanthidin. After each infusion, samples were obtained and analyzed as in Group I.

Group III: Ten dogs were studied as an open chest preparation. An electromagnetic flow probe was placed in the left coronary artery as close to its origin as possible, and coronary flow was measured using a Carolina Medical Electronics flowmeter. A sampling catheter was sutured into the coronary sinus. Another catheter was placed in the right atrium by way of the right external jugular vein. A right femoral arterial catheter was inserted to monitor arterial blood pressure.

Acetyl strophanthidin, 0.05 mg/kg in 5 ml of saline solution, was injected into the right atrium. Blood samples were then obtained simultaneously from the coronary sinus and femoral artery at 2, 4, 6, 8, 10, 12, 20 and 30 minutes. After a 2½ hour interval, the same dose of acetyl strophanthidin was administered in a similar manner simultaneously with 7 ml of 25 percent magnesium sulfate. Blood sampling was repeated in the same manner.

Results

Group I. The administration of magnesium sulfate alone resulted in a prompt drop in arterial potassium concentration of 0.34 ± 0.17 mEq/liter ($P < 0.01$) (Table I, Fig. 1). There was no significant transmyocardial potassium gradient after administration of magnesium sulfate. In addition, there were no significant changes in serum sodium or calcium concentration. The administration of magnesium sulfate usually resulted in a transient decrease in mean blood pressure of 20 to 30 mm Hg.

Groups II and III: The administration of acetyl strophanthidin was associated with a myocardial egress of potassium as determined by a positive coronary sinus-femoral artery potassium concentration difference (Tables II and III, Fig. 2 and 3). The 15 acetyl strophanthidin infusions in Groups II and III were pooled for analysis. The mean of the maximal differences in coronary sinus-femoral artery potassium concentration which occurred between 2 and 8 minutes after the first administra-

TABLE II

Group II: Potassium Concentrations*

	Coronary Sinus	SE	Femoral Artery	SE	Coronary Sinus-Femoral Artery
Control					
1	3.6	0.12	3.6	0.13	0
2	3.7	0.13	3.6	0.14	0.1
Acetyl strophanthidin, 1					
2 minutes	4.6	0.18	4.2	0.14	0.4
4 minutes	4.5	0.18	4.3	0.15	0.3
6 minutes	4.4	0.17	4.1	0.12	0.3
8 minutes	4.2	0.14	4.1	0.19	0.1
12 minutes	4.2	0.18	4.0	0.11	0.2
20 minutes	3.8	0.18	3.9	0.10	−0.1
30 minutes	3.7	0.18	3.8	0.10	−0.1
Control					
1	3.9	0.28	3.8	0.19	0.1
2	3.9	0.24	3.8	0.20	0.1
Acetyl strophanthidin, 2					
2 minutes	4.8	0.22	4.3	0.24	0.5
4 minutes	5.1	0.25	4.6	0.22	0.5
6 minutes	5.1	0.26	4.7	0.22	0.4
8 minutes	5.2	0.17	4.7	0.25	0.5
12 minutes	5.0	0.27	4.8	0.26	0.2
20 minutes	4.5	0.31	4.7	0.31	−0.2
30 minutes	4.4	0.34	4.5	0.37	−0.1
Control					
1	5.0	0.55	4.8	0.50	0.2
2	4.9	0.49	4.8	0.20	0.1
Acetyl strophanthidin + magnesium sulfate					
2 minutes	5.4	0.36	5.3	0.40	0.1
4 minutes	5.6	0.52	5.4	0.33	0.2
6 minutes	5.3	0.45	5.2	0.32	0.1
8 minutes	5.2	0.45	5.1	0.32	0.1
12 minutes	4.8	0.17	4.7	0.17	0.1
20 minutes	4.4	0.19	4.7	0.15	−0.3
30 minutes	4.4	0.19	4.4	0.18	0

* Mean coronary sinus and arterial potassium concentration ±1 SEM (mEq/liter) and the concentration differences after serial acetyl strophanthidin infusions at 2½ hour intervals with magnesium sulfate ($MgSO_4$) given simultaneously with the third dose of acetyl strophanthidin. Average of 6 dogs.

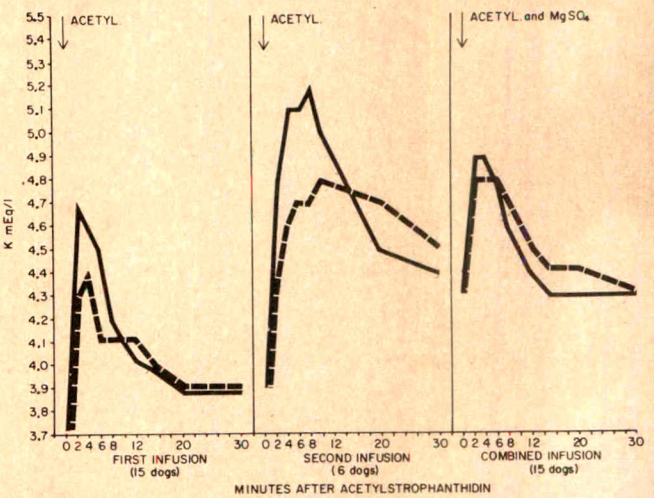

Figure 2. Mean potassium concentration in coronary sinus and arterial blood after serial infusions, 2½ hours apart, of 1.0 mg of acetyl strophanthidin with 7 ml of 25 percent magnesium sulfate given with the third acetylstrophanthidin dose. **Broken line** = arterial blood level; **solid line** = coronary sinus level.

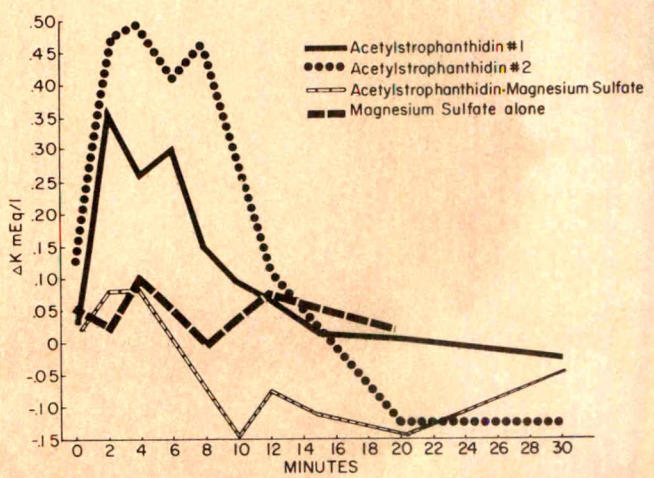

Figure 3. Transmyocardial potassium gradient (coronary sinus-arterial) after acetyl strophanthidin alone, acetyl strophanthidin and magnesium sulfate ($MgSO_4$), and magnesium sulfate alone.

TABLE III

Group III: Potassium Concentrations*

	Coronary Sinus	SE	Femoral Artery	SE	Coronary Sinus-Femoral Artery
Control					
1	3.7	0.06	3.7	0.08	0
2	3.7	0.16	3.6	0.14	0.1
Acetyl strophanthidin					
2 minutes	4.7	0.12	4.3	0.12	0.4
4 minutes	4.7	0.17	4.4	0.18	0.3
6 minutes	4.5	0.14	4.1	0.11	0.4
8 minutes	4.2	0.12	4.1	0.13	0.1
10 minutes	4.1	0.10	4.0	0.13	0.1
12 minutes	4.1	0.11	4.0	0.12	0.1
15 minutes	4.0	0.10	4.0	0.14	0
20 minutes	4.0	0.09	3.9	0.10	0.1
30 minutes	4.0	0.14	4.0	0.17	0.1
Control					
1	3.8	0.26	3.8	0.28	0
2	3.8	0.20	3.8	0.29	0
Acetyl strophanthidin + magnesium sulfate					
2 minutes	4.5	0.16	4.5	0.17	0
4 minutes	4.6	0.11	4.5	0.16	0.1
6 minutes	4.5	0.19	4.5	0.11	0
8 minutes	4.3	0.14	4.5	0.16	−0.2
10 minutes	4.2	0.16	4.4	0.14	−0.2
12 minutes	4.1	0.19	4.3	0.18	−0.2
15 minutes	4.1	0.10	4.2	0.13	−0.1
20 minutes	4.2	0.16	4.2	0.18	0
30 minutes	4.3	0.25	4.3	0.28	0

* Mean coronary sinus and arterial potassium concentrations (mEq/liter) and the concentration differences after administration of acetyl strophanthidin alone and after administration of acetyl strophanthidin plus magnesium sulfate ($MgSO_4$). Average ± SEM for 10 dogs.

tion of acetyl strophanthidin was 0.47 ± 0.22 mEq/liter (SD) (Fig. 4).

In Group II, the second dose of acetyl strophanthidin was associated with a significantly greater potassium egress than the first dose (Fig. 2 and 3). The mean of the maximal differences in potassium concentration which occurred from 2 to 8 minutes after acetyl strophanthidin was 0.80 ± 0.35 mEq/liter (SD) (Fig. 4). Statistical analysis confirmed that the means of the maximal coronary sinus-femoral artery potassium differences after administration of acetyl strophanthidin alone in Groups II and III were different from the control differences ($P < 0.05$) and from zero ($P < 0.05$).

In Groups II and III, when acetyl strophanthidin was given simultaneously with magnesium sulfate, there was no significant egress of myocardial potassium. The mean of the maximal coronary sinus-femoral artery potassium differences was 0.15 ± 0.24 mEq/liter (SD), which was not statistically different from the control differences (Fig. 4). The time at which the maximal differences occurred varied, but was most commonly observed 2 to 4 minutes after the injection of acetyl strophanthidin (Tables II and III, Fig. 2 and 3).

Coronary flow had no relation to the maximal potassium gradient. Flow increased transiently after the administration of magnesium sulfate but returned to control levels within 2 minutes. Coronary flow, as might be expected, occasionally decreased during arrhythmias but had no consistent relation to the potassium flux. Blood pressure usually increased transiently after the administration of acetyl strophanthidin. There were no consistent changes in sodium or calcium induced by the administration of acetyl strophanthidin alone or in combination with magnesium sulfate.

Discussion

This study confirms the observation that digitalis glycosides cause an egress of potassium from the myocardium.[12–16] Egress is perhaps a misnomer in that egress of potassium from the myocardium which occurs during systole is only slightly augmented by cardiac glycosides, but the expected reentry of potassium during cardiac repolarization is markedly impeded.[17] Acetyl stro-

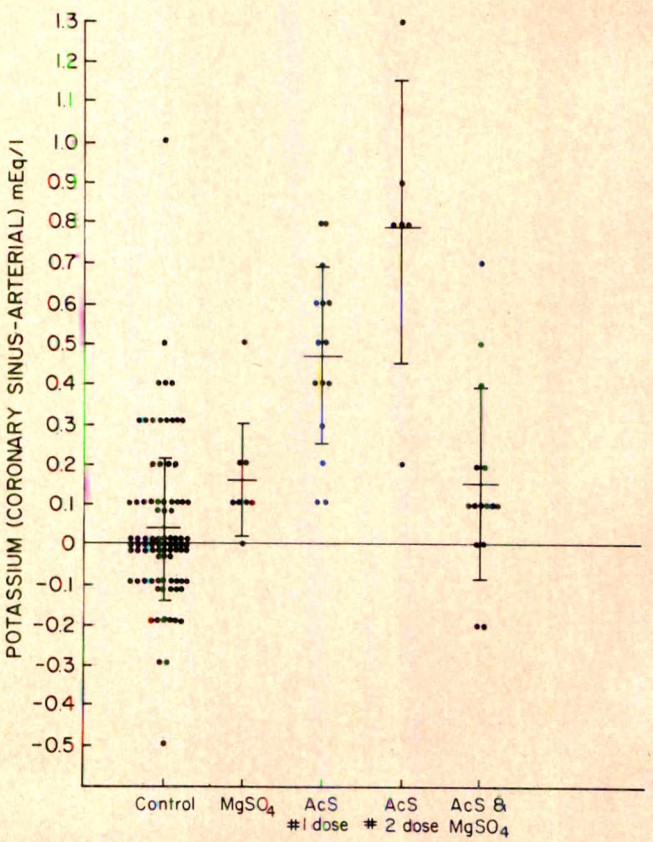

Figure 4. Mean of the maximal differences (±SD) in potassium concentration (coronary sinus-arterial) during control periods, after administration of magnesium sulfate ($MgSO_4$) alone, first dose of acetyl strophanthidin (AcS), second dose of acetyl strophanthidin and acetyl strophanthidin plus magnesium sulfate.

phanthidin inhibits the activity of the sodium–potassium-dependent membrane ATPase which is responsible for the transmembrane concentration gradients of sodium and potassium.[3,4] The inhibition of this ATPase impedes the active "pumping" of potassium back into the cell against the concentration gradient.

Hypokalemia sensitizes the myocardium to the toxic effects of digitalis.[18,19] Studies have often focused on the easily measured level of potassium in the serum, although it is recognized that cellular depletion may exist in the face of normal or even high serum levels.[18] The administration of potassium salts has been shown to be effective therapy for the arrhythmias of digitalis toxicity.[20] Glynn[4] has suggested that increased extracellular concentration of potassium may counteract the digitalis-induced inhibition of membrane ATPase. However, in the presence of normal serum potassium levels, the administration of potassium salts may not be helpful and, on occasion, may be harmful.[21,22] Congestive heart failure,[6] myocardial infarction,[7] myocardial ischemia,[23] hypomagnesemia,[5] diuretic drugs,[8,9] and the administration of digitalis preparations[10] have all been reported to lead to a loss of myocardial potassium.

Digitalis-induced arrhythmias and loss of myocardial potassium: Many investigators have suggested an etiologic relation between the loss of myocardial potassium induced by digitalis and the development of digitoxic arrhythmias; others have not concurred. Grupp and Charles[17] showed that digitalis-induced arrhythmias occurred before the myocardium had lost a significant quantity of potassium. They also observed that sinus rhythm returned when myocardial potassium deficit was maximal. This led them to suggest that the development of arrhythmias was dependent on transient potassium gradients which developed across the cell membrane. Regan et al.[23] demonstrated that with ventricular ischemia or administration of acetyl strophanthidin, myocardial potassium loss preceded the development of arrhythmias. They also showed that infusion of potassium chloride into the coronary artery, which rapidly increased extracellular potassium concentrations, produced the same type of arrhythmias. Pretreatment with procainamide or glucose and insulin blocked the development of arrhythmias and the loss of potassium from the myocardium. Some investigators[24] have shown that quinidine reduces the loss of myocardial potassium; others[25] have demonstrated that, despite its antiarrhythmic effect, quinidine potentiates the digitalis-induced myocardial potassium egress. Other investigators[14] found that pretreatment with reserpine was effective in blocking digitalis-induced arrhythmias but not the myocardial potassium loss. One of the most impressive studies suggesting that there is a causal relation between the loss of myocardial potassium and the development of arrhythmias was presented by Helfant et al.[13] They demonstrated that digitalis-induced arrhythmias are associated with myocardial potassium egress and that treatment of digitoxic arrhythmias with diphenylhydantoin leads to correction of arrhythmias and prompt reversal of potassium egress.

In our studies, although myocardial potassium egress usually occurred after the administration of acetyl strophanthidin alone, egress was not always related to the development of arrhythmias. There was no constant relation between myocardial potassium loss and the development of arrhythmias. In groups II and III after the first infusion of acetyl strophanthidin, arrhythmias occurred in 8 of 15 studies. All arrhythmias but 1 (7 of 15) were associated with potassium egress. Three of the 15 animals had no arrhythmias despite significant potassium egress. A third (5 of 15) had no arrhythmias and no statistically significant potassium egress. In all 6 studies in which acetyl strophanthidin was administered a second time, arrhythmias occurred and potassium egress was marked Most importantly, although the coadministration of magnesium sulfate blocked potassium egress in all studies (15 of 15) arrhythmias still occurred in 9 animals.

In our studies, although most untreated arrhythmias were associated with potassium egress, the latter did not always precede the development of arrhythmias. In addition, magnesium sulfate consistently blocked the egress of myocardial potassium in all studies; despite this blockade, arrhythmias occurred in 60 percent of the animals. The results suggest that, in this study, factors other than potassium egress were operative in the production of the digitalis-induced arrhythmias.

Serum calcium and magnesium: Changes in serum calcium concentration affect myocardial excitability. Hypercalcemia potentiates the development of digitalis toxicity, whereas hypocalcemia inhibits the toxic effects of digitalis preparations.[26] Calcium chelating agents have been recommended for the treatment of digitalis toxicity, but their therapeutic benefits are usually evanescent.[27] No significant changes in serum calcium were observed during the course of our experiments. It is possible that the production of hypermagnesemia may have influenced membrane permeability to calcium, thus accounting for the observed changes in digitalis sensitivity.

Hypomagnesemia and digitoxic arrhythmias: It has been suggested that the early phase of digitalis-induced arrhythmias is related to myocardial potassium loss, whereas larger doses of the type used in this study (1 mg of acetyl strophanthidin) may cause arrhythmias by other mechanisms such as calcium release and catecholamine effect. The results of our study do not provide definitive information concerning the antiarrhythmic action of magnesium sulfate. On the other hand, they demonstrate that, like other antiarrhythmic agents,

such as diphenylhydantoin, glucose and insulin and quinidine, magnesium sulfate can block digitalis-induced myocardial potassium egress.

We have previously shown that hypomagnesemia facilitates the development of digitoxic arrhythmias and, in these instances, magnesium sulfate is a particularly effective antiarrhythmic agent.[2] In isolated heart preparations, the addition of magnesium antagonizes some of the electrophysiologic effects of increased potassium concentration in the bath fluid.[28] Action potential amplitude, action potential duration, resting potential, atrioventricular conduction interval and maximal rate of depolarization are all decreased by increased bath concentrations of potassium. All of these abnormalities are magnified by decreasing the concentration of magnesium in the bath; conversely, they are corrected by increasing the magnesium concentration in the bath fluid.

The egress of myocardial potassium has been attributed to inhibition of membrane ATPase by acetyl strophanthidin. Magnesium is an essential metallocoenzyme for this ATPase, and the presence of excess magnesium may, to some degree, overcome the digitalis-induced blockade of this enzyme. The administration of magnesium sulfate alone resulted in a rapid decrease in arterial potassium concentration, indicating that there was a cellular uptake of potassium. However, magnesium sulfate alone did not result in an influx of myocardial potassium. It is therefore suggested that the effect of magnesium sulfate is essentially one of overcoming the ATPase inhibition induced by digitalis.

Acknowledgment

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Clinical Studies with a Solid State Fiberoptic Oximeter

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A new fiberoptic catheter oximeter with the capability of continuously measuring oxygen saturation and pressure for 72 hours is described. The in vitro calibration and the in vivo evaluation of this catheter appears to be satisfactory with a high correlation coefficient and a standard deviation of less than 2 percent. Problems with catheter size, blood clot formation on the catheter and special care to prevent destruction of the fibers are presented, as well as limitations in interpreting information obtained with this new technique. Despite these limitations, the data warrant the use of such a continuous reading instrument in selected critically ill patients.

Recent reports[1–4] have documented decreased oxygen saturation in central venous and right atrial blood of critically ill patients. It has also been demonstrated that decreased oxygen saturation in right atrial blood coincides with decreasing blood pressure and other signs of progressive cardiogenic shock. All of these studies utilized intermittent sampling of right atrial or central venous blood through a central venous catheter and determination of oxygen saturation by a standard spectrophotometric method. These data suggest that a means of continuously monitoring mixed venous oxygen saturation might provide a clinically useful technique for evaluating acutely ill patients with cardiovascular disease. This paper describes a monitoring system suitable for the continuous measurement of oxygen saturation for up to 72 hours in acutely ill patients, which does not require withdrawal of blood samples or heparinization of the patient.

Methods and Materials

Description of the Instrument

Fiberoptic catheter oximeter instruments have been developed and used clinically.[5–7] The solid state fiberoptic catheter oximeter used in this study has been previously described by Johnson et al,[8] and a diagram of it is presented in Figure 1. The unit utilizes the spectrophotometric method using reflected light from whole blood for determining oxygen saturation; its basic principle is summarized in the equation:

$$\text{Oxygen saturation} = A - B\frac{e_i}{e_r}$$

where A and B are constants dependent on catheter geometry and the red blood cell absorption and scattering properties, e_i is the intensity of reflected infrared light and e_r the intensity of reflected red light.

Three sets of intermeshed fiberoptic bundles are located in the wall of a No. 7 French intravascular catheter. Two sets of fiberoptic bundles transmit red and infrared light to the tip of the catheter; a third set of fibers transmits light reflected from blood at the tip of the catheter back

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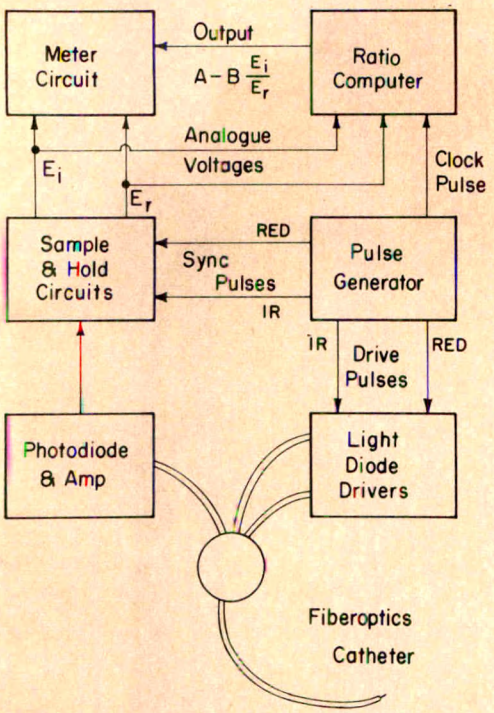

Figure 1. Block diagram of the fiberoptic oximeter instrument.

to a photodetector. A pulse generator develops a 200 Hz square-wave pulse train which triggers the driving circuits for the light-emitting diodes. The diodes are pulsed alternately, producing 2 separate channels of red and infrared wavelengths, respectively. The spectral width of the light-emitting diodes is approximately 40 nanometers, centered at 685 and 925 nanometers. The pulse generator also sends synchronous pulses to sample and hold circuits so that when the red light emitting diode is turned on, a channel to the red circuit is opened, and when the infrared light-emitting diode is turned on, a channel to the infrared circuit is open. Reflected red and infrared light returning from the blood is detected, amplified and sent to sample-and-hold circuits. The outputs of the sample-and-hold circuits are therefore 2 analog voltages corresponding to the levels of red and infrared reflectance. The ratio between these 2 reflectance levels is proportional to the oxygen saturation. A direct conversion to saturation can be made by introducing A and B constants which are determined from the slope and intercept of the regression equation correlating the infrared-to-red ratio with oxygen saturation.

Catheters for this study were fabricated from commercially available radiopaque polyethylene material. A no. 4 French catheter was passed through the lumen of a no. 7 French catheter. Approximately 100 fiberoptic glass strands, diameter 0.002 inch, were placed in the wall between the 2 catheters. The distal end of the catheters and the fiberglass bundles were firmly sealed with epoxy, and the distal tip was smoothly polished. There was no protective cage used over the distal tip. The proximal lumen of the inner (no. 4 French) catheter was connected to a Leur-Lok fitting, and the fiberoptic strands were separated into 3 bundles and coupled to the light emitting diodes and photodetector. Twenty-five fibers transmit light from the infrared diode, 25 fibers transmit light from the red diode, and 50 fibers transmit light reflected from the blood at the distal tip of the catheter to a photodetector.

In Vitro Calibration

Extensive studies performed previously in this laboratory have determined the effect of blood pH, hematocrit and temperature on the in vitro calibration of the fiberoptic oximeter. Results of these tests reported by Johnson et al.[8] documented that the calibration of the oximeter using the 2 wavelengths method is independent of blood temperature and essentially independent of hematocrit variations between 40 and 60 percent. Little change was observed in instrument calibration until hematocrit dropped below 30 percent. The oxygen saturation was found to shift approximately 1 percent for each 0.1 pH unit deviation from the normal pH of 7.4 in blood. On the basis of these results a simpler experimental setup than those previously described was used for the in vitro calibration of the catheters used in this study. As shown in Figure 2, blood is pumped through a disc oxygenator where gas exchange occurs. Tygon tubing carries blood from the oxygenator back to the roller pump, and the catheter is inserted into a fitting in the Tygon tubing.

Human red blood cells were used for the in vitro calibration experiments. The cells were first diluted with Hartman's lactated Ringer's solution to obtain a hematocrit of approximately 40 percent. Blood pH was maintained at 7.4 throughout each calibration run by adding small amounts of sodium bicarbonate or varying the percent of carbon dioxide in the total gas mixture used to oxygenate or reduce the blood. The reliability of this preparation has been previously documented. The oxygen saturation was varied by altering the ratio of nitrogen and oxygen in the inflow gas while maintaining the carbon dioxide at 4 percent in order to minimize pH changes. Using this system, oxygen saturation levels from 1 to 100 percent were obtained. Samples were drawn through the central lumen of the fiberoptic catheter and correlated with values obtained with the fiberoptic oximeter system. Drawn samples were analyzed for pH, pO_2 and pCO_2 in an Instrument Laboratory blood gas analyzer. The percent oxygen saturation

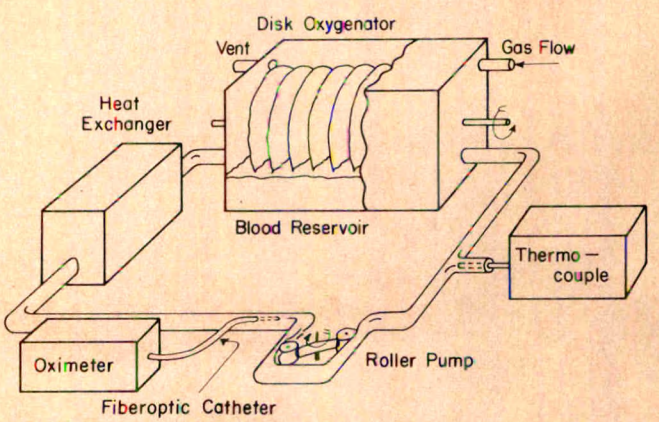

Figure 2. Blood flow system for in vitro calibration. Blood is pumped through tubing and past the fiberoptic catheter tip by a roller pump. Gas exchange occurs in the disc oxygenator.

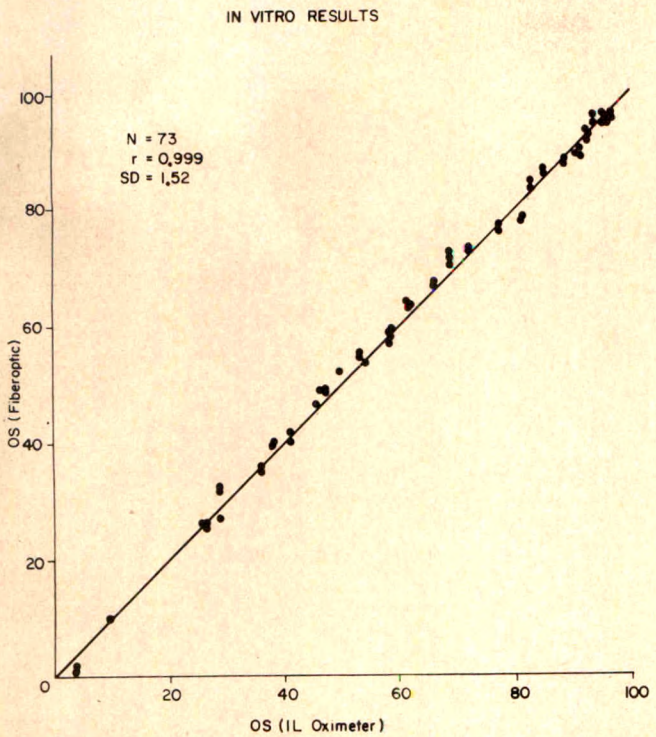

Figure 3. Correlation between the oxygen saturation determined by the fiberoptic oximeter and simultaneously drawn samples analyzed by the CO-Oximeter (in vitro results).

was determined with the Instrument Laboratory 182 CO-Oximeter. The CO-Oximeter employs the 3 wavelengths method (548, 568 and 578 nanometers) for the spectrophotometric determination of oxyhemoglobin, carboxyhemoglobin and total hemoglobin. The reliability of the CO-Oximeter compared with the manometric Van Slyke analysis of oxygen saturation has been previously documented.[9,10] The CO-Oximeter used in this study was compared with ten Van Slyke determinations between 65 and 100 percent saturation with an observed standard deviation of 1 percent saturation. Therefore, it may be concluded that the results of the CO-Oximeter are accurate over the physiologic range of hemoglobin oxygen saturation. Due to its ease in obtaining percent saturation, this technique was used for calibrating the fiberoptic oximeter. Nine fiberoptic catheters were calibrated in this test system.

In Vivo Calibration and Evaluation

Following the in vitro calibration studies, in vivo evaluation was carried out in the cardiac catheterization laboratory and the cardiovascular surgery operating room and postoperative intensive care units. The fiberoptic catheters were cleaned and sterilized with ethylene oxide in the routine manner. Six studies were performed in patients undergoing open heart surgery. Preoperatively, the catheter was passed from a cutdown on the median basilic vein to the superior vena cava. The catheter remained in the superior vena cava throughout the operative procedure and immediate postoperative period, and oxygen saturation was recorded continuously with the fiberoptic catheter. Samples were drawn intermittently through the lumen of the fiberoptic catheter, and oxygen saturation was determined immediately on the CO-Oximeter. This provided multiple data points over a wide range of pH and hemoglobin, correlating saturation determined by the fiberoptic system and the CO-Oximeter.

Four studies were performed in the cardiac catheterization laboratory. After routine right heart catheterization, the fiberoptic catheter was passed from the median basilic vein cutdown through the right atrium and into the inferior vena cava to the level of the renal veins. The catheter was then slowly withdrawn and simultaneous measurements were obtained from the fiberoptic oximeter and samples drawn through the central lumen. The variation in saturation between inferior and superior vena cava provided additional data points in the physiologic range of venous oxygen saturation.

The time of catheter placement varied from 30 minutes in the catheterization laboratory to 72 hours in the postoperative intensive care unit. The average time of catheter placement was 12 hours. Blood clot formation on the distal tip of the catheter was prevented by intermittent flushing with dilute heparin solution. There was no significant drift in base line or calibration with prolonged use.

Results

The results of the in vitro calibration experiments are shown in Figure 3. The correlation between oxygen saturation measured with the CO-Oximeter and oxygen saturation calculated with the fiberoptic catheter was 0.99 for 73 samples over a saturation range of 1.6 to 97 percent. The standard deviation is 1.52 percent saturation. The in vivo evaluation of the fiberoptic catheter is presented in Figure 4. The correlation between oxy-

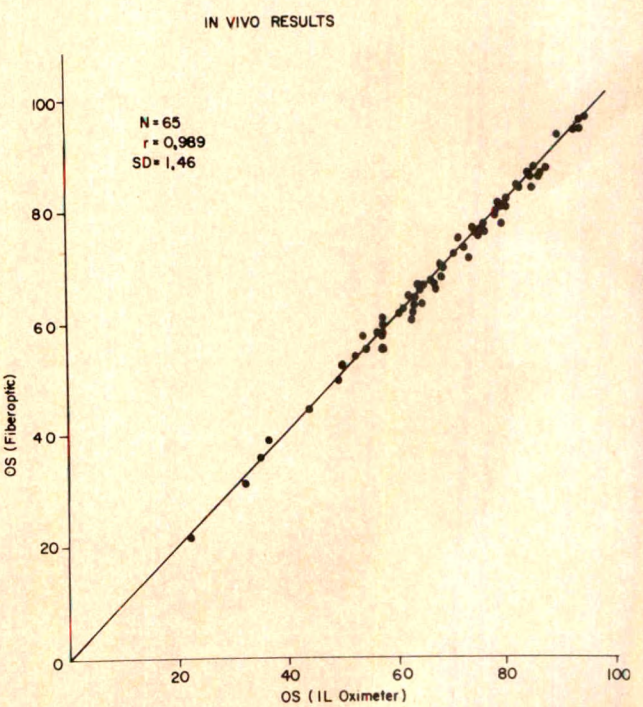

Figure 4. Correlation between the oxygen saturation determined by the fiberoptic oximeter and simultaneously drawn samples analyzed by the CO-Oximeter (in vivo results).

TABLE I

Illustrative Case

Sample	Time	Venous Oxygen Saturation (%) Fiberoptic Oximeter	Venous Oxygen Saturation (%) I.L. Oximeter	Hb (g)	Arterial pO_2 (mm Hg)
(Day 1)					
1	10:00 AM	22.0	21.51	13.4	27
2	10:30 AM	32.0	31.01	13.9	36
3	10:50 AM	36.5	38.92	13.6	36
4	11:30 AM	49.8	49.47	...	...
5	11:50 AM	69.6	71.23	13.4	37
6	12:15 PM	52.2	55.2	13.0	...
Patient on pump at 12:30 PM					
7	1:00 PM	86.0	80.48	8.5	...
8	1:30 PM	87.4	85.87	10.2	...
9	1:50 PM	83.4	83.76	10.1	535
10	2:20 PM	86.2	87.45	10.8	...
11	2:40 PM	85.3	85.87	11.0	...
12	3:05 PM	90.9	93.25	11.7	261
13	4:00 PM	80.4	77.43	12.0	250
Patient in intensive care unit					
14	10:00 PM	72.3	74.79	14.1	137
(Day 2)					
15	10:00 AM	69.4	67.93	...	76
16	1:45 PM	63.8	61.60	13.2	164
(Day 3)					
17	9:00 PM	58.2	59.49	12.4	153
(Day 4)					
18	8:00 AM	50.6	52.11	11.8	56

Hb = hemoglobin; I.L. = Instrument Laboratory CO-Oximeter.

gen saturation determined by the CO-Oximeter and the fiberoptic catheter is 0.989 for 65 samples over an oxygen saturation range from 22 to 96 percent. The standard deviation is 1.46 percent. The hemoglobin ranged from 9.0 to 16.0 g/100 ml, and pH from 7.2 to 7.5 in these in vivo studies. Two in vivo data points with 5 percent oxygen saturation difference from the CO-Oximeter were excluded from the above tabulation, due to the fact that the hemoglobin value fell below 9 g/100 ml in both cases.

Illustrative case: The following case demonstrates the potential usefulness of this monitoring system in a 31 year old white woman admitted for repair of tetralogy of Fallot. Past history included Blalock-Taussig procedures at the ages of 6 and 9 years. In 1969 progressive dyspnea developed as well as other signs of congestive failure and syncopal episodes suggestive of hypoxia. Arterial hypoxia was so severe that attempts at pulmonary function testing in the preoperative period produced a hypoxic convulsion when the patient attempted to perform a vital capacity test. She was brought to the operating room on June 24, 1970 with minimal premedication. Anesthesia was induced with Diazepam, and a 4N arterial catheter was placed percutaneously in the dorsalis pedis artery. The fiberoptic catheter was inserted in the left median basilic vein and passed into the superior vena cava. Initial saturation in the superior vena cava was 22 percent (Table I). At this time the arterial pO_2 was 27 mm Hg. Anesthesia was maintained at this time with methoxyflurane and oxygen. Thirty minutes later runs of spike trains appeared on the electroencephalogram and appeared to be the electrical correlate of seizure activity. However, at this time the superior vena cava saturation had increased to 32 percent and arterial pO_2 to 36 mm Hg. It was therefore believed with this evidence of improved oxygenation during anesthesia and surgery that the electroencephalogram probably did not signal serious hypoxia, and the operation was continued with repeated arterial pO_2 and oxygen saturation determinations (Table I). The maintenance of a relatively adequate venous oxygen saturation in spite of a recent stormy cardiovascular course was reassuring. In the immediate postoperative period, the venous oxygen saturation increased to 80 percent (sample 13) and was maintained at this level for the next 18 hours.

On the first postoperative day (day 2) an endotracheal tube was left in place, and the patient's condition remained stable with controlled ventilation. The mixed venous saturation during this time ranged from 64 to 69 percent. Extubation was carried out on the second postoperative day (day 3). However, signs of systemic hypoxia, marked primarily by various arrhythmias, were accompanied by a fall in venous oxygen saturation to 58 percent. After reintubation, venous oxygen saturation increased, and the patient's clinical condition improved. Extubation was again performed on the third postoperative day after an arterial pO_2 of 153 had been obtained, and the mixed venous oxygen saturation remained stable at approximately 60 percent. However, after extubation the arterial pO_2 decreased to 56 and the mixed venous saturation decreased to 51 percent. Both of these values were increased by the administration of 100 percent oxygen by mask, and extubation was finally tolerated. The fiberoptic catheter was removed on the fourth postoperative day. A small deposit of fibrin was noted on the tip of the catheter, but the sample drawn through the central lumen and determined on the CO-Oximeter was still within 1.5 percent of the saturation recorded through the fiberoptic system. The patient's course over the next 2 weeks required a tracheostomy and intensive long-term ventilatory care. However, she was discharged 3 weeks after operation.

Discussion

Potential advantages and limitations of methods: Although the fiberoptic oximeter described in this report has several unique features, potential disadvantages must also be anticipated. A practical problem concerns the size of the catheter used in this study. A no. 7 French catheter usually requires a venous cutdown procedure. In patients undergoing cardiopulmonary bypass or diagnostic cardiac catheterization, this disadvantage was easily justified. However, in patients not undergoing major surgery, a venous cutdown may be more difficult to justify. A catheter of this size might also be expected to produce a relatively high incidence of sterile thrombophlebitis if left in place more than 72 hours. However, improved catheter design with proper selection of catheter material

should permit the construction of a no. 5 French catheter while still retaining a central lumen suitable for measuring pressure and withdrawing samples. A catheter of this size could be introduced through a needle or mylar sheath and would also cause less trauma to the vascular system. Not reported in our data but of significance are 2 patients in whom the catheter could not be advanced to a suitable position. In 1 case this was due to an inability to pass the catheter from a median basilic vein because of previous cutdowns, and in the second case, inability to pass the catheter beyond the axilla. In both cases measurement of superior vena cava pressure was made by way of a subclavian vein puncture.

Blood clot formation on the catheter is also a potential disadvantage. If the catheter is flushed at a regular interval or slowly infused with a dilute heparin solution, clotting was not apparent in this study. The wide clinical use of central venous catheters without significant clotting problems also indicates that with reasonable care, clotting can be avoided. A monitoring system for detecting blood clot formation at the tip of the catheter has been developed. In vivo studies performed in dogs have demonstrated that as a blood clot forms on the tip of the catheter, the levels of red and infrared reflected light decrease gradually. At the same time the normal fluctuations of the reflected light levels due to pulsatile blood flow are reduced. Thus the observation of a reduced light level with reduced amplitude fluctuations indicates the formation of a clot.

A third potential complication is the occurrence of artifactual readings if the catheter tip impinges on the vessel wall. However, this is easily detected by unusually high levels of reflected light with loss of the normal fluctuations of the reflected levels. Normal signals return when the catheter is repositioned.

Damage to the catheter with disruption of the fiberoptic bundles is obviously a serious potential problem. In 1 case after placement of the cardiopulmonary bypass cannula for drainage of the superior vena cava, occlusion of the superior vena cava by an externally placed tape produced enough pressure on the wall of the fiberoptic catheter to break the glass fiberoptic bundles with resultant loss of the signal. This was of no clinical threat since the outer and inner polyethylene catheters held the glass fibers in place, and the catheter was retrieved intact. On another occasion, a bend of the catheter external to the patient resulted in disruption of the fibers and loss of signal. Therefore, the catheter, although usable in the routine clinical situation, does require reasonable care and manipulation. Subsequent tests using plastic fiberoptics have shown no loss of signal despite significant catheter manipulation. No problems were encountered with the catheter-to-instrument junction and the electronic system remained stable throughout the studies.

Clinical interpretation of data: Caution must be used in the clinical interpretation of the data provided by this new technique. Venous oxygen saturation depends on at least 3 factors: oxygen saturation of arterial blood, the cardiac output, and the ability of the red blood cells to deliver oxygen to peripheral tissues. Thus, a decreased venous oxygen saturation may result from arterial hypoxia, inadequate cardiac output relative to tissue needs, or a rightward shift of the oxygen dissociation curve and increased delivery of oxygen to the periphery.

The location of sampling is also of considerable importance. True mixed venous blood can only be accurately obtained from the pulmonary artery. Differences in oxygen saturation between superior and inferior vena caval blood and streaming of blood in the right atrium impair quantitative assessment of this index proximal to the pulmonary artery. However, recent evidence indicates that changes in oxygen saturation of samples obtained from the superior vena cava and right atrium reflect in both direction and magnitude changes similar to those obtained in samples from the pulmonary artery.[2] This discrepancy between samples obtained from the superior vena cava and pulmonary artery is apparently due to redistribution of blood flow in the presence of a low cardiac output with a higher percentage of the cardiac output perfusing the brain and heart. Thus, the oxygen saturation of blood returning from the brain is maintained at more nearly normal levels during low flow states. Some increased extraction of oxygen occurs from blood perfusing the arms. The mixing of components from the head and arms produces a decrease in saturation of blood sampled in the superior vena cava but not as great a decrease as in mixed venous samples. It is also concluded that samples obtained from the right atrium would be clearly preferable to samples obtained from the superior vena cava in monitoring acutely ill patients.

Clinical applications: Although sampling from the pulmonary artery would be preferable to right atrial or superior vena caval sampling, the continuous display of oxygen saturation from the right atrium or even from the superior vena cava is of considerable value. This technique provides rapid and reliable information. The 2 most commonly encountered causes of decreased venous oxygen saturation are decreased cardiac output and arterial hypoxemia. Both conditions may require rapid therapeutic intervention, particularly during the intraoperative period or in the intensive care unit. In addition to alerting the clinician to these problems, the continuous recording of oxygen saturation provides an index for following the response to therapeutic manipulations such as

the administration of oxygen to correct arterial hypoxemia or inotropic agents to increase cardiac output. Even with the potential complications discussed, the information obtained from the continuous measurement of central venous oxygen saturation is a valuable extension of the ability to monitor the overall status of acutely ill patients. The fiberoptic catheter described in this paper has worked satisfactorily in a limited number of patients and is currently being introduced into routine clinical practice. However, its ultimate value is yet to be determined.

Acknowledgment

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Reliability and Normal Variations of Computer Analysis of Frank Electrocardiogram by Smith-Hyde Program (1968 Version)

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A preliminary assessment was made of automated electrocardiographic signal recording and telephone transmission for recording on magnetic tape and subsequent "off-line" computer analysis by the initial Smith-Hyde program (1968) of the Frank X, Y and Z leads in 334 healthy persons and 39 cardiac patients obtained from 2 hospital populations in Seattle. The Smith-Hyde analytical program provided an over-all sensitivity of 76 percent for true positives (abnormal electrocardiograms) and specificity of 75 percent for true negatives (normal electrocardiograms) for predominantly normal case material used in this study. Although 25 percent were misclassified, the ratio of correct to incorrect classifications was 3.0 for all items, and ranged from 4.7 to 61.2 for various diagnostic categories. Angular components of the quantified normal electrocardiogram showed less variation than voltage magnitudes, and bimodal distributions for initial and terminal QRS forces (ROR_3 and RER_4) were found only in the frontal plane when differences in sex and age were disregarded. There were more significant differences in voltage magnitudes of ventricular repolarization than of either atrial or ventricular depolarization in relation to sex and age of healthy persons.

Before determining to use the Smith-Hyde program*[1] for digital computer analysis of the Frank electrocardiogram, the operational performance of the program was investigated. Appropriate recording equipment was rented for clinical trial in 2 hospitals, and reels of magnetic tape were mailed to a computer center that had placed this program in daily operation.[2] Clinical reliability of computer diagnosis was assessed by comparison of analytical reports with clinical interpretation of a 12 lead scalar electrocardiogram. [Visual interpretation of the 12 lead electrocardiogram was performed by 2 of us (RAB and SRY) utilizing essentially Grant's orientation for electrocardiographic diagnosis.] The normal range of variation for many electrocardiographic items was determined from satisfactory recordings and analyses of clinically normal electrocardiograms obtained from 216 healthy middle-aged persons. Results of this study have relevance for electrocardiographic field studies which require "off-line" computer analy-

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* The Smith-Hyde program is a digital computer program for wave recognition, rhythm analysis and contour analysis in spatial magnitude (rho), and 3 planar angles and magnitudes of selected successive vectors in consecutive P, QRS, and T complexes of a 10 second sample of modified Frank X, Y and Z orthogonal lead signals recorded simultaneously. Representative values for similar complexes are combined and reported as averaged values; significant deviations of isolated beats are detected and reported. The program was developed in FORTRAN for processing on an IBM 1800 data processing system, either directly "on-line" or subsequently "off-line" as an individual user option.

TABLE I

Computer Analysis of Electrocardiograms

A. Computer Analysis

	Group Health Hospital	University Hospital	Both Hospitals
Normal	96	140	236 (63%)
Abnormal	43	94	137 (37%)
Totals	139	234	373 (38% of 974)
Percent Normal	69%	60%	63%

B. Computer Analysis vs. Clinical Interpretation

	Clinical Interpretation	
	Abnormal	Normal
Computer analysis and classification		
Abnormal	64 true positives	73 false positives
Normal	20 false negatives	216 true negatives

Sensitivity for true positives = 76%. Specificity for true negatives = 75%.
Rates of correct to incorrect classification = 280/93 = 3.0.
Chi square = 70.47, df = 1, $P < 0.0001$.

sis by this program; they also provide a base line for evaluation of subsequent improvements in this program which was released for study purposes in 1968.

Material and Methods

Clinical electrocardiograms were recorded in 373 persons aged 15 to 74 years who had been examined by physicians at the University Hospital or Group Health Hospital in Seattle and who were found to be free of cardiovascular or other major disease. Electrocardiograms were also recorded in 39 patients with known cardiac disease at the University Hospital. The 12 conventional leads, plus 3 orthogonal leads of the Frank system were recorded, 3 leads at a time, by a programmed Marquette electrocardiograph. This was equipped with independently buffered preamplifiers for each lead; direct-coupling provided a flat frequency response from 0 to 100 Hz. Conventional scalar projections were recorded directly on paper, while the same signals were transmitted by telephone (with use of a private line at Group Health Hospital and a switchboard at University Hospital) to a magnetic tape recorder in another part of the city. Reels of ¼ inch magnetic tape were sent by air mail to Omaha, Nebraska for batched data processing of 10-second samples of X, Y and Z leads on an IBM 1800 computer[2] utilizing the Smith-Hyde program released in 1968.[1] The quality of direct telephone transmission from the recorder in Seattle to the computer in Omaha revealed no faults in systems operation from either recording site. Analyses of the following were printed on paper and punched on Hollerith cards: noise level, rhythm, heart rate, conduction times, diagnostic statements and matrix of spatial magnitudes ("rho"), frontal, sagittal and horizontal angles and voltage magnitudes of 30 components of the P, QRS and T forces. Data in these 2 formats were returned by mail to Seattle for comparison with clinical interpretations. A "conversational computer statistical system"[3] developed for the IBM 1130 data processor was used for statistical analysis of the data, excluding analyses of electrocardiographic recordings in which background noise level exceeded 33 μv at the patient.

For comparison with computer analysis, paper tracings and computer reports were classified as negative or positive for one or more items. Criteria for evaluation included the following:

1. Essentially the same rhythm, allowing for minor discrepancies in terminology for variations in supraventricular rhythms.
2. Heart rate within 10 beats/min of the rate recorded on the paper tracing.
3. Occurrence of premature beats of any focus.
4. Significant differences in atrioventricular or intraventricular conduction of importance to clinical diagnosis.
5. Similarity of QRS voltage, that is, low, normal or high.
6. QRS deformities consistent with myocardial infarction and significant axis deviation.
7. Significant changes in ST–T forces of ventricular repolarization, that is, strain, pericarditis, ischemia, digitalis effect, and the like.

When there was agreement in several items but disagreement in one or more other items, classification of "false positive" or "false negative" was based upon the more significant findings. For example, if there was agreement in rhythm, rate, conduction and voltage, failure of the computer to identify definite evidence, by clinical interpretation of the tracing, of myocardial infarction was designated "false negative." Conversely, when the computer interpretation indicated one or more premature beats, yet inspection of the same X, Y and Z leads used for processing showed no change in mechanism, it was classified as "false positive."

Variations in magnitude of electrocardiographic items in 216 healthy persons were expressed as percentage relations of standard deviations to corresponding means. In the case of angular data, standard deviations were related to 360° (circumference of a circle) to avoid misleading percentages whenever the observed means happened to be near zero degrees. In a few instances data on some electrocardiographic items were missing.

Results

Reliability of computer analysis: Combining data on 2 hospital populations provided 236 cases of 373 (63 percent) with normal electrocardiograms, and 137 (37 percent) with a variety of electrocardiographic abnormalities by computer analysis (Table I). In all instances the paper tracings revealed signals of good quality; the background noise level on these tracings was 15.5 ± 3.6 μv by computer analysis.

Only 216 of the 236 normal records, as determined by computer, were also normal by clinical interpretation and, therefore, "true negatives" (Table I). Twenty records that were abnormal by clinical interpretation represented "false nega-

tives." Similarly, only 64 of the 137 computer determined abnormal records were "true positives." and 73 were "false positives" in relation to clinical interpretation. Representative examples are illustrated in Figures 1 and 2. Thus, the sensitivity for true positives was 76 percent, and the specificity for true negatives was 75 percent. Concomitantly 93, or 25 percent, were misclassified by computer analysis. The ratio of correct to incorrect was 70.47 (df = 1, $P < 0.0001$). In 16 random instances the computer analysis was repeated immediately after the initial analysis with no change in

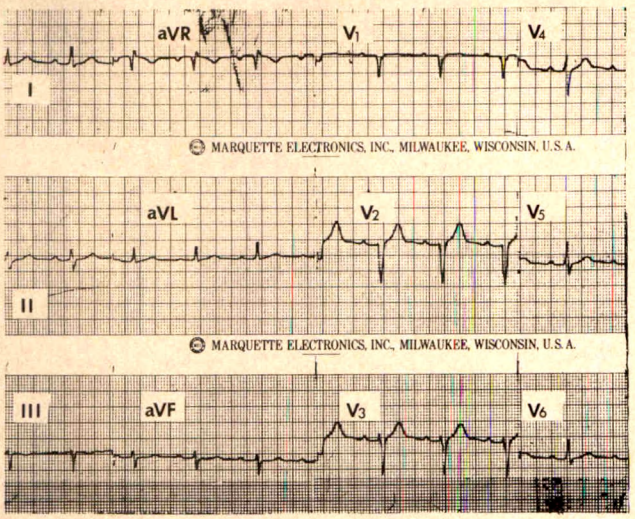

Figure 1. Example of a "true positive" computer report of an electrocardiogram exhibiting a conduction defect and anteroseptal myocardial infarction. Note that in Figures 1 to 4 noise level reported at "12 millivolts" at the computer represents 12 μv at the patient.

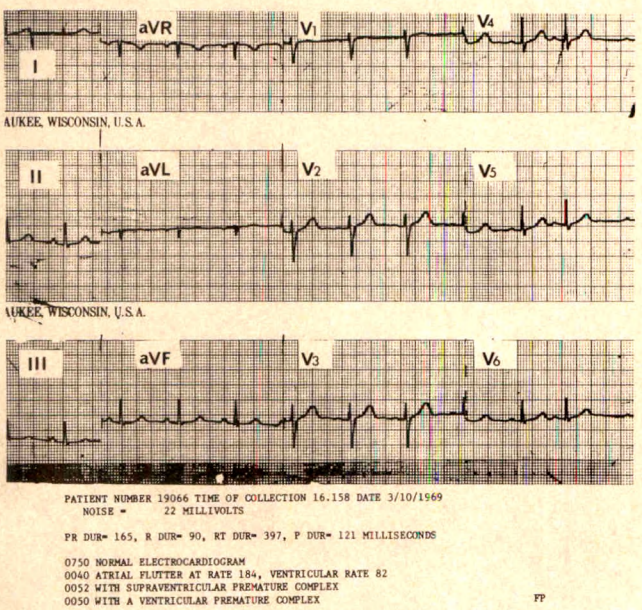

Figure 3. Example of a "false positive" computer report of an electrocardiogram exhibiting normal sinus rhythm and a supraventricular (probably atrial) premature beat (leads V_4 to V_6) but neither atrial flutter nor a ventricular premature beat.

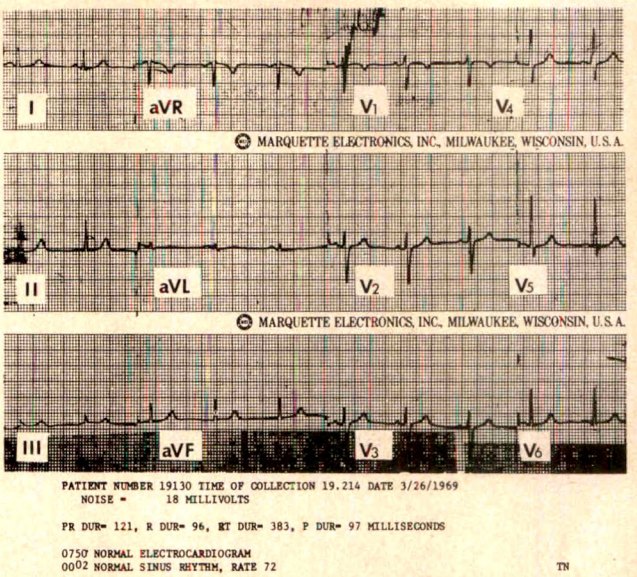

Figure 2. Example of a "true negative" computer report of a normal electrocardiogram.

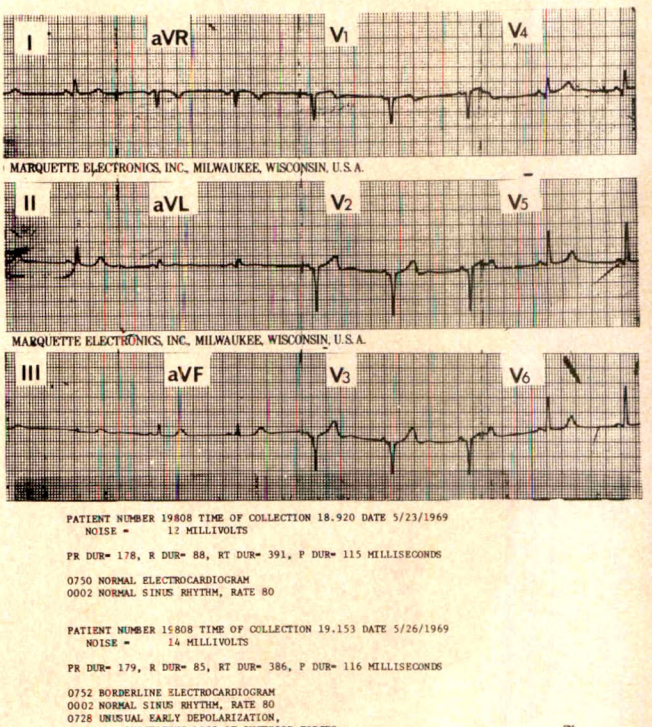

Figure 4. Example of a "false negative" computer report of an electrocardiogram exhibiting (clinically) changes consistent with old anteroseptal infarction, but reported as "normal" initially, and "borderline normal with usual early depolarization suggesting loss of inferior forces" when the analysis was immediately repeated.

TABLE II

Comparison of Computer Analysis with Clinical Interpretation of Normal versus 6 Categories of Abnormal Electrocardiographic Items in 344 Individuals from 2 Hospital Populations in Seattle

A. Clinical Interpretation Before Computer Analysis

Off-line computer analysis	Entirely Normal ECG	Arrhythmias (Premature Beats, Rate Disparity)	Conduction Disorders (A–V or I–V)	Voltage Abnormalities (Low or Increased)	Axis Deviations (RAD or LAD)	Myocardial Infarctions (Anterior or Inferior)	Repolarization Abnormalities (S–T, T, Q–T)
Normal ECG (Overall)	216 True Negatives	5	5	5	3	7	1
Arrhythmias (including rate disparity, premature beats)	60	14					
Conduction disorders (A–V or I–V)	1	12					
Voltage abnormalities (low or increased)	26	9		True Positives			
Axis deviations (RAD or LAD)	3				8		
Myocardial infarctions (anterior or inferior)	5					14	
Repolarization abnormalities (S–T, T, Q–T)	12					1	13

False Negatives

B. Analytical Performance of Smith-Hyde Program Released in 1968

Off-line Computer Analysis	Sensitivity $\frac{TP \times 100, \%}{TP + FN}$	Specificity $\frac{TN \times 100, \%}{FP + TN}$	Correct Classification / Incorrect Classification $\frac{TP + TN, \text{Ratio}}{FN + TP}$	Chi Square	P
Normal ECG (overall)	76	75	3.0	70.	<0.0001
Arrhythmia (including rate disparity, premature beats)	74	83	4.7	33.	<0.0001
Conduction disorders (A–V or I–V)	71	99.7	61.0	218.	<0.0001
Voltage abnormalities (low or increased)	64	92.8	11.0	45.	<0.0001
Axis deviation (RAD or LAD)	73	99.2	61.2	87.	<0.0001
Myocardial infarction (anterior or inferior)	67	98.6	30.1	37.	<0.0001
Repolarization abnormalities (S–T, T or Q–T)	93	96.7	27.7	180.	<0.0001

A–V = atrioventricular; ECG = electrocardiogram; I–V = intraventricular; LAD = left axis deviation; RAD = right axis deviation.

electrodes or clinical recording. In 5 of these 16 cases (31 percent) the computer analysis changed significantly on normal or abnormal classification. These findings indicate the risk of error when healthy persons with normal electrocardiograms are screened by this program, and the need for clinical checking of every report to assure quality control.

Further analysis revealed appreciable differences in program performance in various diagnostic categories of computer analysis (Table II). The most frequent source of false positive computer analysis was reporting of arrhythmias; in 48 cases premature beats were reported when none was apparent by clinical interpretation of the same sample of X, Y and Z leads. Atrial or A–V nodal rhythm and atrial flutter or fibrillation were correctly diagnosed. In a few instances heart rate was incorrectly measured, with differences ranging from 40 to 100 beats/min. The most frequent source of false negative computer analysis was failure to detect clinically apparent evidence of myocardial infarction. Representative examples of false classifications are shown in Figures 3 and 4. Prevalence of other types of false positives and false negatives are indicated in Table II. The ratio of correct to incorrect classifications ranged from 4.7 for arrhythmias to 61.2 for atrioventricular or intraventricular conduction disorders. Accordingly, the specificity for true negatives was higher for any one of these categories than for all categories in the entire electrocardiogram. These findings indicate both the considerable diagnostic power of the Smith-Hyde program and the need for confirmation by clinical interpretation to assure quality control.

TABLE III

Comparison of Heart Rates and Interval Measurements* in Healthy Persons

	Clinical Interpretation	Computer Analysis
Heart rate (beats/min)	69 ± 11 (16%)	71 ± 14 (19%)
P–R (msec)	167 ± 24 (14%)	156 ± 19 (12%)
QRS (msec)	73 ± 10 (14%)	91 ± 9 (10%)
Q–T (msec)	379 ± 29 (8%)	393 ± 27 (7%)

* Means, standard deviations (and coefficients of variation).

In several instances multiple differences were noted between computer analysis and clinical interpretation for the same person. Accordingly, the sum of true positive, false positive and false negative items according to electrocardiographic information categories exceed the number of subjects classified in these groups.

Normal variation in computer measurements of electrocardiographic components: Statistical data on heart rate, conduction times (P–R and QRS intervals) and duration of electrical systole (designated R–T interval) for 216 normal electrocardiograms are shown in Table III. Similar data on spatial magnitudes and planar angles of selected P, QRS and T components analyzed by the program are presented in Table IV and Figure 5. Items that showed less variation than heart rate were P–R, QRS and R–T intervals and almost all planar angles. Items that exhibited greater variation than heart rate included frontal plane angles of initial ROR_3 (for the first 30 msec) and terminal RER_4 (for the last 40 msec) of QRS forces, and

TABLE IV

Spatial Magnitudes and Planar Angles of Electrocardiographic Forces in Healthy Persons (Means, Standard Deviations, Coefficients of Variation*)

	Spatial Magnitude	Planar Angles		
		Frontal	Sagittal	Horizontal
P1, 2	93 ± 40 (43%)	280 ± 46 (17%)	284 ± 49 (17%)	75 ± 94 (124%)
P3, 4	87 ± 30 (35%)	295 ± 37 (13%)	270 ± 33 (12%)	84 ± 40 (47%)
PP	88 ± 32 (6%)	289 ± 38 (13%)	279 ± 36 (13%)	73 ± 57 (78%)
ROR_3	119 ± 41 (34%)	113 ± 47 (42%)	187 ± 162 (87%)	179 ± 164 (91%)
		300 ± 35 (12%)		
RR	350 ± 106 (30%)	318 ± 34 (11%)	251 ± 31 (12%)	104 ± 24 (23%)
RMax	1374 ± 327 (24%)	320 ± 30 (9%)	264 ± 28 (11%)	94 ± 23 (25%)
RER_4	503 ± 193 (38%)	72 ± 58 (80%)	215 ± 34 (16%)	143 ± 35 (25%)
		308 ± 34 (11%)		
T_2	72 ± 39 (55%)	259 ± 90 (35%)	266 ± 120 (45%)	93 ± 125 (134%)
T_4	155 ± 75 (48%)	294 ± 72 (25%)	301 ± 78 (26%)	52 ± 65 (125%)
T_6	405 ± 147 (36%)	317 ± 13 (4%)	309 ± 20 (6%)	54 ± 27 (50%)
T_8	150 ± 68 (46%)	307 ± 36 (12%)	299 ± 36 (12%)	56 ± 29 (52%)

* 100 (standard deviation)/mean for voltage magnitudes.
100 (standard deviation)/360 for planar angles, except 180 used in cases of bimodal distributions.

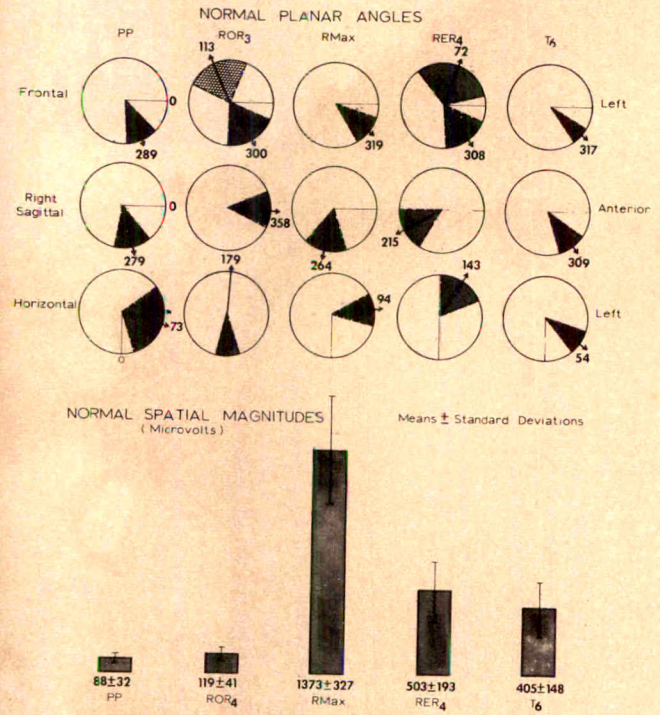

Figure 5. **Top,** statistical data for vectors of mean P (PP), initial 30 msec of QRS (ROR_8), maximal R voltage (RMax), terminal 40 msec of QRS (RER_4) and maximal T voltage (T_6) in frontal, right sagittal and horizontal planes in 216 normal subjects. Mean values of each are cited in degrees, zero reference is indicated for PP diagrams; shaded zeros represent variance of plus and minus one standard deviation. See text for comments about bimodal distributions. **Bottom,** corresponding values for spatial magnitudes of same items expressed in microvolts.

T_2 (second of 8 consecutive parts of the R–T interval) of early ventricular repolarization. All spatial magnitudes of these normal subjects had greater variation than most of the planar angles. Bimodal distributions were observed in initial QRS forces (ROR_3) and terminal QRS forces (RER_4) of the frontal plane projections. Although the majority of normal tracings were reported to have ROR_3 angles ranging from 0° to 270° in the *frontal* plane, none was interpreted by the Smith-Hyde program as showing myocardial infarction or other abnormalities of ventricular depolarization. Although RER_4 angles in the frontal plane were widely distributed, none was interpreted by this program to have terminal force abnormalities such as right or left axis deviation. In contrast, there was very little variation for either mean or maximal R angles in all 3 planes.

Normal electrocardiograms obtained from 216 healthy male and female patients were subdivided according to the patient's age into 3 groups: under 30, from 30 to 44, and over 44 years of age for detection of significant differences in relation to both sex and age (Table V). With respect to atrial depolarization, only the horizontal planar magnitude of the mean P voltage exhibited a difference ($P < 0.01$) between men and women in the oldest age group. For purposes of data reduction, QRS items for ROR_3 RMax and RER_4, rather than R_1 through R_8 inclusive, were selected for analysis. Only the frontal planar angle of ROR_3 differed slightly in the youngest men and women ($P < 0.05$). In regard to RMax, younger men had

TABLE V
Significant Differences in Electrocardiographic Items of Healthy Persons in Relation to Age and Sex*

Item	Age Group (yr)	Men (means ± SD)	Women (means ± SD)	P Value
HM, PP	>44	45 ± 16	35 ± 13	<0.01
FA, ROR_3	<30	162 ± 81	222 ± 88	<0.05
RHO, RMX	<30	1728 ± 292	1413 ± 314	<0.01
FM, RMX	<30	1613 ± 337	1365 ± 344	<0.05
HM, RMX	<30	1357 ± 229	992 ± 261	<0.001
HM, RMX	>44	1157 ± 253	1033 ± 261	<0.05
RHO, RER_4	<30	683 ± 159	543 ± 190	<0.05
SA, RER_4	<30	208 ± 24	231 ± 31	<0.05
SM, RER_4	<30	574 ± 171	429 ± 125	<0.01
HM, RER_4	<30	605 ± 156	420 ± 169	<0.001
RHO, T_2	<30	120 ± 48	51 ± 21	<0.0001
FM, T_2	<30	68 ± 42	34 ± 18	<0.001
SM, T_2	<30	106 ± 43	47 ± 19	<0.0001
HM, T_2	<30	110 ± 44	39 ± 23	<0.0001
RHO, T_2	30–44	84 ± 26	52 ± 26	<0.0001
SA, T_2	30–44	320 ± 66	272 ± 98	<0.05
SM, T_2	30–44	75 ± 25	46 ± 25	<0.0001
HA, T_2	30–44	40 ± 66	116 ± 126	<0.01
HM, T_2	30–44	75 ± 27	39 ± 24	<0.0001
RHO, T_2	>44	81 ± 34	59 ± 35	<0.0001
FA, T_2	>44	260 ± 93	220 ± 100	<0.05
SA, T_2	>44	278 ± 119	212 ± 142	<0.01
SM, T_2	>44	73 ± 30	55 ± 35	<0.01
HM, T_2	>44	72 ± 33	47 ± 25	<0.0001
RHO, T_6	<30	643 ± 152	363 ± 102	<0.0001
FM, T_6	<30	542 ± 139	342 ± 95	<0.0001
SA, T_6	<30	315 ± 9	294 ± 16	<0.0001
SM, T_6	<30	489 ± 124	255 ± 95	<0.0001
HA, T_6	<30	50 ± 9	68 ± 15	<0.0001
HM, T_6	<30	536 ± 136	279 ± 84	<0.0001
RHO, T_6	30–44	444 ± 81	355 ± 129	<0.01
FA, T_6	30–44	319 ± 7	314 ± 9	<0.05
SA, T_6	30–44	311 ± 16	295 ± 21	<0.01
SM, T_6	30–44	339 ± 87	273 ± 107	<0.05
HA, T_6	30–44	52 ± 17	63 ± 19	<0.05
HM, T_6	30–44	371 ± 74	268 ± 105	<0.001
RHO, T_6	>44	440 ± 146	316 ± 111	<0.0001
FM, T_6	>44	327 ± 129	274 ± 99	<0.05
SA, T_6	>44	323 ± 14	305 ± 20	<0.0001
SM, T_6	>44	359 ± 123	245 ± 93	<0.0001
HM, T_6	>44	383 ± 134	247 ± 96	<0.0001

* Similar differences were found in RHO and most of the planar angles for T_3 to T_5, inclusive; in addition FM showed significant differences between sexes in persons over 30 years of age, whereas SA and HA differed in persons under 30 years of age.

greater spatial, frontal planar and horizontal planar magnitudes than younger women; the greatest difference was found in the horizontal plane (HM, ROR_3, $P < 0.001$). Similarly, the oldest men had slightly greater horizontal planar magnitudes than the oldest women. As for terminal QRS forces, RER_4, similar differences were observed in only the youngest age group (Table V).

There were many highly significant differences between voltage magnitudes of T_2 through T_7 in all age groups. Again for purposes of data reduction, only values for T_2 (representing S–T segment) and T_6 (peak of T forces) are shown in Table V. In addition, frontal, horizontal and sagittal angles of these forces also exhibited significant differences between the 2 sexes in all 3 age groups.

The trends in relation to effects of aging on spatial magnitudes are illustrated in Figure 6 for atrial and ventricular repolarization and in Figure 7 for ventricular repolarization. Clearly, younger men have greater magnitudes of RMax and T_6 vectors than either older men or women of any age group.

These differences reveal the greater discriminatory power of items of ventricular repolarization than depolarization by this program of computer analysis. Furthermore, they indicate the necessity of having several sets of normal standards according to both age and sex when quantitative differences in abnormal tracings are to be interpreted.

Discussion

Both sensitivity and specificity with this initial version of the Smith-Hyde program showed performance levels that would not be satisfactory for routine, unsupervised clinical usage. Occurrence of both false positive and false negative analyses clearly indicated an urgent need for continued surveillance of all records by a cardiologist to assure quality control. Since Smith and colleagues have subsequently made numerous improvements and revisions in this program, the results of this study cannot be used to assess operational performance with the extensively revised program. Nevertheless, these data provide a base line by which the degree of improvement in subsequent revisions of the program might be assessed.

If computer analyses are not carefully checked by a physician, there is a risk of generating iatrogenic or "computerogenic heart disease" and attendant anxiety of a patient.[5] Conversely, there is a smaller risk of significant error when a false negative computer analysis disregards appropriate evidence of myocardial infarction.

Analysis of variation of items of diagnostic importance revealed apparent discrepancies. A bimodal distribution of initial QRS forces (ROR_3) for the first 30 msec in frontal plane angles was unexpected by selection of normal case material, and not correlated with computer program interpretation of normal electrocardiograms. Similar magnitudes of variation did not occur in the sagittal or horizontal planes. Since the initial ROR_3 vector is normally perpendicular to the frontal plane, it is apparent that minor deviations in projection of this vector in frontal plane are widely dispersed. Recognition by computer programs of initial force abnormalities such as myocardial infarction should rest primarily upon deviations beyond a narrow range of vector projections in sagittal and horizontal planes.

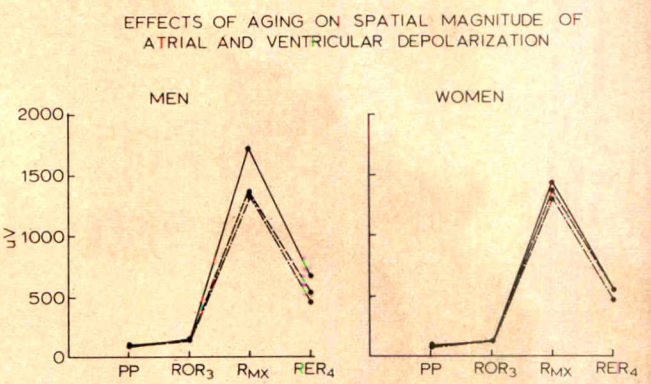

Figure 6. Variations in mean spatial magnitudes of mean atrial depolarization (PP), initial (ROR_3), maximal (RMax), and terminal (RER_4) ventricular depolarization forces in relation to age and sex in healthy persons.

In accord with prior observations by Pipberger and Pipberger[6] of higher computer diagnostic recognition rates for instantaneous vectors than various magnitudes of QRS complexes, there was less variation with planar angles than with spatial magnitudes in normal subjects when differences in age and sex were disregarded. Conversely, there were more significant differences in magnitudes than in angles in relation to sex in all age groups of normal persons. These differences seemed to reflect the greater mass and volume of the heart in men than in women, particularly in younger adults. Similar quantitative differences for ΣQRS and ΣT measurements of the 12 lead electrocardiogram were also reported by Simonson.[7]

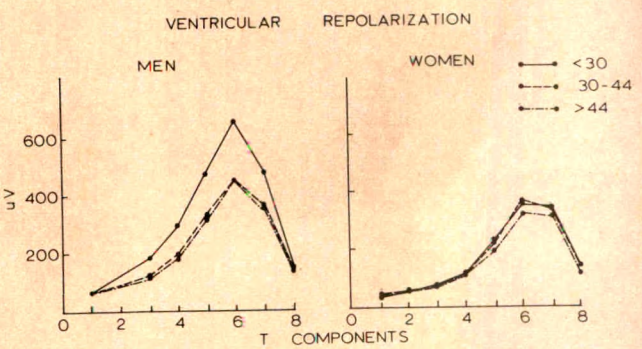

Figure 7. Variations in mean spatial magnitudes of 8 components of ventricular repolarization in relation to age and sex of healthy persons.

When operational use of the Smith-Hyde program is verified by visual interpretation of the tracings by an experienced physician or cardiologist to assure quality control, the matrix of quantitative data provided by this program could permit development of computer program techniques for assessment of serial changes in consecutive recordings on the same patients.

Acknowledgment

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Effect of Sotalol on Clinical Arrhythmias

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Sotalol (MJ 1999) was administered to 20 patients for the treatment of 22 episodes of supraventricular and 6 episodes of ventricular arrhythmias. The dose range was 9 to 50 mg intravenously and 20 to 80 mg orally given every 6 hours. In 4 of 6 patients supraventricular tachycardia was converted to normal sinus rhythm. In 4 with episodic supraventricular tachycardia, Sotalol prevented further recurrences in all. In 1 patient atrial flutter was converted to normal sinus rhythm. In 3 others with atrial flutter, and in 3 with atrial fibrillation, Sotalol slowed the ventricular response from an average rate of 125 to 72 beats/min. In 1 patient with episodic atrial fibrillation and another with episodic ventricular tachycardia, Sotalol prevented further recurrences. In 1 of 2 patients Sotalol decreased the frequency of premature atrial contractions; in 5 patients with premature ventricular contractions, it abolished them in 2 and reduced their frequency in the other 3. Side effects included transient hypotension in 3 patients and bradycardia sufficient to require reducing the dose of Sotalol in 4. It is concluded that Sotalol is a moderately effective antiarrhythmic drug which may be preferable to other beta adrenergic blocking agents because of its lack of substantial myocardial depressant effects.

Beta adrenergic blocking agents, such as propranolol, are being used with increasing frequency for the treatment of clinical cardiac arrhythmias.[1,2] One of the potentially serious side effects of such drugs is their direct production of myocardial depression which can precipitate or worsen congestive heart failure.[3,4] Sotalol® (MJ 1999) is a newer beta adrenergic blocking agent which produces less myocardial depression than propranolol[5–7]; it thus might be a safer drug to use in patients with heart failure if it is as effective in the treatment of arrhythmias.

Although Sotalol antagonizes experimental arrhythmias produced by epinephrine[8] as does propranolol,[1] it is not a local anesthetic agent and may be less effective than propranolol in preventing ouabain-induced arrhythmias.[9] Furthermore, directionally opposite effects on intracellular action potentials suggest that Sotalol and propranolol may have different antiarrhythmic effects, aside from their beta blocking properties.[10]

The present study was undertaken in a group of patients with a variety of atrial and ventricular arrhythmias to evaluate the clinical effectiveness of Sotalol as an antiarrhythmic agent.

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TABLE I

Intravenously Administered Sotalol

Case no.	Age (yr) & Sex	Arrhythmia Origin	Arrhythmia Type	Dose of Sotalol (mg)	Effect
1	56M	ASHD	SVT	20	No effect
2	70M	RHD	PVC	20	PVC abolished
3	28M	PHD	SVT	20	No effect
4	75M	ASHD	SVT	12	NSR
5	57F	ASHD	A Fl	9	NSR
6	58F	ASHD	SVT	20	NSR
7	66F	Acute MI	SVT	10	NSR
8	72M	Acute MI	SVT	20	NSR
9	82F	ASHD	A Fl	35	Slowing of HR
10	61M	Acute MI	PVC, PAC	40	Decreased
11	58M	PHD	A Fl	50	Slowing of HR
12	82M	ASHD	A Fl	16	Slowing of HR
13	46M	ASHD	PAC	10	No effect
14	87F	ASHD	A Fib	20	Slowing of HR

A Fib = atrial fibrillation; A Fl = atrial flutter; ASHD = arteriosclerotic heart disease; HR = heart rate; MI = myocardial infarction; NSR = normal sinus rhythm; PAC = premature atrial contraction; PHD = primary heart disease; PVC = premature ventricular contraction; RHD = rheumatic heart disease; SVT = supraventricular tachycardia.

Methods

All patients were hospitalized at the time of the initial administration of Sotalol, and were evaluated by history, physical examination, electrocardiogram and chest roentgenogram. Tables I and II contain a description of each patient, the type of arrhythmia, the dose of Sotalol given and the effect obtained. Of a total of 20 patients, 14 were given Sotalol intravenously for an acute arrhythmia (Table I). Four of these patients and 6 additional patients received Sotalol orally as prophylactic therapy for recurrent arrhythmias (Table II). Four patients thus appear in both tables. Fifteen patients had coronary artery disease (3 with acute myocardial infarction), 2 rheumatic heart disease, 1 primary myocardial disease and 1 hypertension with the "sick sinus" syndrome. Sotalol was given intravenously in a bolus of 2 to 10 mg every 5 minutes as required, with an average total dose of 21 mg (range 9 to 40 mg). During intravenous administration, the electrocardiogram was continuously monitored and rhythm strips were obtained at frequent intervals. The average oral dose of Sotalol was 160 mg (range 80 to 320 mg/day) administered in 4 divided doses. If patients were receiving other antiarrhythmic drugs, these were discontinued before administration of Sotalol. Patients receiving maintenance doses of digitalis continued to receive the same doses. Sotalol was not administered to pregnant women, patients with bronchial asthma, or those with a high degree of atrioventricular (A–V) block.

Results

Sotalol, Acute Therapy

A summary of the results is listed in Table III. Effects were noted within 1 to 5 minutes of the last dose of Sotalol.

Supraventricular tachycardia: In 4 of 6 patients, conversion to sinus rhythm occurred, and there was no effect on the rhythm of 2 patients. The dose of Sotalol ranged from 10 to 20 mg.

Atrial flutter: Sotalol produced conversion to normal sinus rhythm in 1 of 4 patients; a decrease in ventricular rate was achieved in the other 3 by increasing the A–V block. The dose of Sotalol ranged from 9 to 50 mg. Figure 1 illustrates the results of a dose of 6 mg of Sotalol given intravenously to a 57 year old woman with atrial flutter associated with an acute myocardial infarction. After slowing of the ventricular response there was conversion to normal sinus rhythm.

Atrial fibrillation: In 3 patients, Sotalol produced an increase in A–V block which slowed the ventricular rate from an average value of 125 to 72 beats/min and resulted in clinical improvement in each patient.

Premature ventricular contractions: These were abolished in 2 patients and decreased from an average of 8/min to 2/min in the 3 remaining patients. The effects lasted for periods ranging from 10 minutes to 5 hours.

Premature atrial contractions: In 1 of the 2 patients Sotalol decreased the frequency of the premature beats; in the other it had no effect.

Sotalol, Chronic Therapy

The effects of orally administered Sotalol on the frequency of recurrent episodic arrhythmias are

TABLE II

Orally Administered Sotalol

Case no.	Age (yr) & Sex	Arrhythmia Origin	Arrhythmia Type	Dose of Sotalol (mg/6 hours)	Effect
1	56M	ASHD	SVT	40	No recurrence, 6 mo
6	58F	ASHD	SVT	80	No recurrence, 6 mo
10	61M	ASHD; acute MI	PVC	20–60	Frequency of PVC's reduced
14	87F	ASHD	A Fib	40	Reduced ventricular rate
15	55F	RHD	SVT, PAC	40	No recurrence, 7 mo
16	64F	ASHD	A Fib	40	Reduced ventricular rate
17	62M	ASHD	VT	40	No recurrence, 6 mo
18	71F	ASHD	PVC	40	Frequency of PVC's reduced
19	75M	ASHD	SVT, PVC	40	No effect
20	72F	Hypertension; "sick sinus" syndrome	A Fib	20	No recurrence, 6 mo

VT = ventricular tachycardia; other abbreviations as in Table I.

listed in Table II. Three of 4 patients with paroxysmal supraventricular tachycardia have not had a recurrence during an average follow-up period of 6 months. One patient each with recurrent atrial fibrillation and ventricular tachycardia, had their recurrent arrhythmias abolished over an average follow-up period of 6 months. Two patients with chronic atrial fibrillation who were receiving digitalis were given supplemental doses of Sotalol to control their ventricular rate since they were prone to digitalis toxicity. The oral dose of Sotalol ranged from 20 to 80 mg 4 times a day.

Side Effects

Side effects were relatively minor. Although all patients showed a slowing of heart rate, there was no detectable evidence of a worsening of congestive heart failure. Bradycardia occurred in 4 patients and was controlled by reducing the dose of Sotalol. Three patients receiving Sotalol intravenously experienced a transient decrease of 16 mm Hg in systemic blood pressure, which was clinically insignificant. One patient receiving Sotalol orally complained of breast discomfort which cleared spontaneously although administration of Sotalol was continued.

Discussion

The results of our study indicate that Sotalol is a moderately effective antiarrhythmic agent for certain arrhythmias. When given orally, it was effective in preventing further episodes of recurrent tachyarrhythmias. When given intravenously, it was moderately effective in controlling supraventricular arrhythmias, by either conversion to normal sinus rhythm or reduction of the ventricular response by increasing the degree of A–V block. Although the number of patients treated were few, our results suggest that the antiarrhythmic spectrum of Sotalol is similar to that of propranolol.[1,2]

Mechanism of antiarrhythmic effects: One mechanism responsible for the antiarrhythmic effects of Sotalol is its beta adrenergic blocking effect. This is best exemplified by the increase in A–V block which results in a decrease in the ventricular response to atrial tachyarrhythmias. It is not known whether Sotalol has other antiarrhythmic effects unrelated to beta blockade. Although Sotalol is devoid of the nonspecific antiarrhythmic effects seen with other beta blocking agents,[8,9,11] studies of its effects on the action potential have shown that it prolongs the action potential duration and the effective refractory period.[10] This latter effect might be responsible for antiarrhythmic actions similar to those of quinidine.[5]

Experimental studies of the antiarrhythmic effects of Sotalol have shown it to be uniformly effective in ventricular arrhythmias induced by hydrocarbon and epinephrine in the dog.[12,13] However, results with arrhythmias produced by coronary artery ligation or infusion of ouabain have been conflicting and may relate to the lack of effect of Sotalol on automaticity.[5,8,11,14]

TABLE III

Summary of Results: Acute Therapy with Sotalol

	Total Cases	Conversion to NSR	Increased A–V Block	Abolished	Decreased	No Effect
SVT	6	4	...	...	...	2
A Fl	4	1	3	...	...	...
A Fib	3	...	3	...	...	...
PVC	5	...	...	2	3	...
PAC	2	...	...	...	1	1

Abbreviations as in Table I.

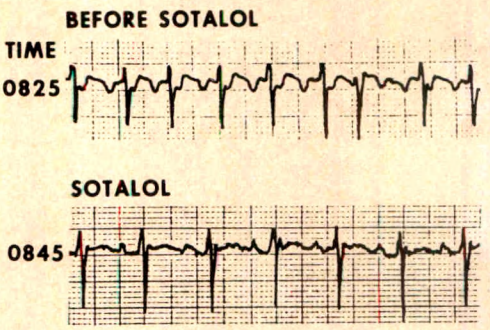

Figure 1. Effects of Sotalol on atrial flutter in a 57 year old woman after an acute myocardial infarction. Administration of 6 mg of Sotalol intravenously successfully converted the flutter to normal sinus rhythm.

Myocardial effects: Several studies have demonstrated the lack of substantial myocardial depressant effects of Sotalol, in both the intact dog[6,15] and man.[16–18] Doses as high as 60 mg/kg of Sotalol have been given to volunteers without incident.[5] Similar results have been obtained in vitro with the rabbit left atrial preparation, in which neither the *d*- nor *l*-optical isomers had any significant effect on the force of contraction despite their markedly different beta blocking properties.[19] Recent studies in the isolated cat papillary muscle not only demonstrated a lack of substantial myocardial depressant effects but also showed that Sotalol produced an increase in force at dose levels of 10^{-4} to 10^{-3} M.[7] This effect was unrelated to intrinsic catecholamine sympathomimetic stores since the same results were obtained in cats depleted of catecholamines by reserpine. In our study, side effects attributable to myocardial depression were minimal, consisting of transient hypotension or bradycardia. However, it must be remembered that even if the direct myocardial depressant effects of Sotalol are minimal, the beta blocking effects may theoretically worsen congestive heart failure in a patient who is greatly dependent on sympathetic stimulation to maintain compensation.[20]

In summary, Sotalol (MJ 1999) appears to be a moderately effective antiarrhythmic agent for arrhythmias of the same general type as those for which propranolol is effective. It has the additional advantage of producing less direct myocardial depression and thus may be preferable in situations associated with borderline or overt congestive heart failure.

Acknowledgment

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Seminar on
Clinical Application of Techniques to Measure Blood Flow in Man. Part III
ALBERTO BENCHIMOL, MD, FACC, Guest Editor

Velocity and Flow Measurements by Electromagnetic Techniques

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In this review of electromagnetic flowmetry, cardiovascular applications of velocity and flow measurements in patients are emphasized. The theory of electromagnetic flowmeters and sequential developments in the field are surveyed in relation to practical problems of utilization of electromagnetic flow devices. The distinction between catheter-tip velocity transducers and catheter flow transducers is discussed. A variety of electromagnetic catheter-tip devices are described, and their potential applicability to patient care is considered.

Development of the electromagnetic flowmeter made it possible to measure the flow of blood continuously, instantaneously and without interference.[1,2] The method has been refined to a readily applicable clinical and investigative tool[3,4] that can be utilized for diagnostic as well as physiologic investigations.[5] The following outline of the principles of electromagnetic flow measurements reviews some of its applications with particular reference to the heart.

Electromagnetic Flowmeters

Principle of operation: The theory of electromagnetic flow measurement has been described and reviewed by others.[6–9] In brief, blood is caused to flow through a magnetic field (Fig. 1). Ions in the plasma, which are moving through the magnetic field, become displaced; negative ions move in the opposite direction of positive ions. An electromagnetic force produced by the negative and positive sides of the bloodstream is sensed by electrodes positioned at right angles to the magnetic field. The electromotive force produced is proportional to the average cross-sectional velocity, and the intensity of the magnetic field according to the following equation[10]:

$$e_O = B\bar{v}d \times 10^{-8} \text{ volts}$$

where e_O is the electromotive force, B the flux density in gauss, $\bar{v}$ the average linear velocity of the liquid in centimeters per second, and d the diameter in centimeters between the electrodes. Instantaneous flow, averaged across the cross section of the vessel, can be measured, as well as instantaneous velocity, since flow equals the product of velocity and cross-sectional area.

Theoretical requirements: The relation between induced electromotive force (e_O) and average cross-sectional velocity ($\bar{v}$) applies even when the fluid velocity is *not* uniform, provided that the profile of flow possesses rotational symmetry about the axis of the tube.[6,7] This result holds for turbulent and laminar regimes provided they possess rotational symmetry.[7] However, any axial asymmetry may severely influence the electrical output.[6,9] A second theoretical requirement (in addition to axial symmetry) is a uniform magnetic field. This may be of practical importance in transducers in which the need for limited size may impose restrictions upon field uniformity.[7]

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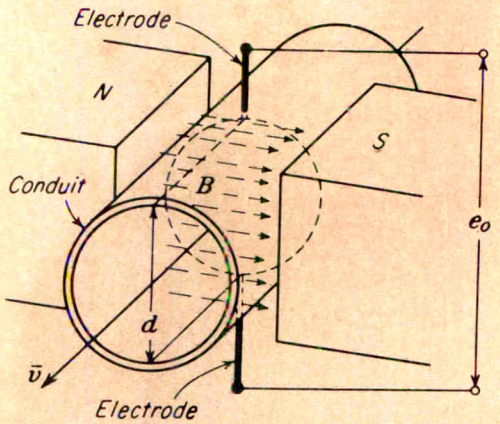


Figure 1. Flow-velocity transducer based upon electromagnetic induction in liquids. Induced electromotive force (e_o) is proportional to magnetic field (B), average linear velocity of blood ($\bar{v}$), and diameter of vessel (d). (Reprinted by permission of McGraw-Hill Book Co. from Instrumentation in Scientific Research by Lion,[9] copyright 1959 by McGraw-Hill Book Co.)

Problems in application: In their least complex form, electromagnetic flowmeters were constructed with a direct-current electromagnet placed about an exteriorized vessel.[1] With such instruments, electrolytic polarization tended to occur at the electrodes[10,11]* To eliminate this difficulty, a flowmeter was designed in which the magnetic field was alternated with a sine wave current source.[10] Alternating magnetic fields introduce the problem of parasitic voltages from capacitive alternating current pick-up and from asymmetric induction in the liquid and in the leads.[9]

Electrical eddy currents and consequent electrode voltages often resulted in zero drift.[12] This problem was circumvented by use of square wave magnetic currents.[12] It can also be overcome by measuring induced current only at the peak intensity of the magnetic field; a gated sine wave flowmeter was developed for this purpose.[13] However, precise adjustment of the gating of some commercial flowmeters has been tedious. Consequently, many investigators have found square wave flowmeters more convenient to utilize. Heat production caused by transducers used with square wave flowmeters has not been a practical problem. For equal amounts of heat produced in the transducer, a square wave current results in lower flow voltages than a sine wave current, because the peak current of a square wave is 40 percent less than that of a sine wave for the same root mean square value.[14] The output voltage, in general, is in the microvolt range.[9]

Flow has been recorded electromagnetically in vessels with an external diameter as small as 1 mm.[15] Pulsatile flow at 60 Hz can be measured with 95 percent accuracy.[16] Harmonic analyses of flow curves indicate that a full response to 20 Hz permits adequate recording of femoral arterial flow in anesthetized dogs.[17] Flow transients of 1 msec duration have been measured, indicating an exceedingly rapid response to changes of flow.[18]

* Electrolytic polarization is the departure of an electrode from its reversible value upon passage of a current.[11]

Perivascular and Cannulating Transducers

Zero flow determination: Theoretically, when the magnetic drive is removed, the flow signal should be zero, and the output of the device should coincide with zero flow as obtained by mechanical occlusion of the vessel to which the transducer is applied. In practice, this does not occur because variable quantities of transformer voltage are detected in the demodulation circuit.[19] This added signal results in a direct-current component in the output which is superimposed on the flow signal.[19] It is possible, however, to build transducers with no significant nonflow component[20,21] or with the nonflow component exactly 90° out of phase with the flow signal.[22] Zero flow under these conditions can be established by turning off the magnetic drive (first type of transducer) or by electrical techniques (second type).[23] Recently, a means of nulling out the transformer and capacitively induced voltages has been developed which gives close correlation between electronic zero and mechanical zero.[19] With most flowmeters, mechanical occlusion of the vessel distal to the transducer has been found to be the only reliable method of producing a valid reference base line.[24,25] Consequently, a variety of occlusive devices have been described.[24–27]

The mean level during diastole of the instantaneous flowmeter signal recorded from the roots of the pulmonary artery or aorta has been widely used as a reference level indicative of zero flow in these vessels.[28] Use of the mean diastolic level of the pulmonary arterial flowmeter appears to permit an accurate measurement of cardiac output, whereas the corresponding portion of the aortic flowmeter signal underestimates cardiac output by 10 percent.[28]

Calibration: Accuracy of calibration of cuff transducers is enhanced if the cuff transducer is calibrated with the same blood[29–31] and preferably the same vessel[31,32] as is used in experimental studies. A decrease in sensitivity of 15 to 50 percent has been observed when blood with 45 to 55 percent hematocrit is used instead of saline solution.[29,30,32] Calibration of cannulating transducers with isotonic saline solution instead of blood causes less inaccuracy than occurs with calibration of cuff transducers; the error is usually reported to be less than 5 percent[33–35] although errors of greater magnitude have been observed.[30,36] The errors that occur in calibration of excised blood vessels with saline solution are related to possible changes in conductivity of the vessels produced by changes in composition of the fluid or vessel wall.[7,32,37] This possibility also explains the value of utilization of the same vessel in a fresh state.[32,38] However, some investigators have found that calibration of cuff flow transducers is independent of the nature or thickness of the vessel.[35,39] In vivo calibration of transducers may circumvent some of the problems of calibration. This can be accomplished by measuring the volume of blood flowing from a vessel in a given time.[40,41] It can also be accomplished by clamping the vessel upstream from the transducer and injecting a known volume of blood through the instrument, at the same time integrating the flowmeter output.[42]

Cuff transducers should have a lumen diameter equal to, or somewhat smaller than, the vessel diameter.[36] The diameter of the vessel may be reduced 20 percent

without perceptibly compromising the normal flow pulse dynamics[36] or mean flow.[43]

Transducers suitable for animal studies: Electromagnetic flow techniques have been used for study of the circulation of animals since 1938.[44] Since the introduction of electromagnetic flow transducers small enough for chronic implantation,[45] a variety of perivascular transducers have been fabricated. Figure 2 shows a schematic diagram of a miniature cuff transducer suitable for measurement of coronary flow in dogs.[29] Inclusion in this type of transducer of a slit and shutter, by tilting the axis of the electrodes approximately 15° from the axis where voltage due to flow would be maximally detected, resulted in a reduction in sensitivity of only 1 percent.[23] Each type of perivascular transducer has specific merits related to size (cuff type), ease of removal (clip-on type) or sensitivity (U type).[46]

Fabrication of miniature transducers has made it possible to measure instantaneous coronary flow even in conscious, unanesthetized animals.[47] Coronary flow in laboratory animals is usually measured by means of a cuff transducer positioned about a short segment of surgically exposed coronary artery.[47] Auto-perfused cannulas have also been developed for measurement of coronary flow in animals with the chest open.[48] Specialized adaptations of transducers have been fabricated for such purposes as measurement of flow through experimentally produced ventricular septal defects[49] or the rings of prosthetic valves in dogs.[50]

Studies in Patients

Functional effects of anastomoses have been demonstrated extensively by direct blood flow measurements in vascular surgery.[51,52] Measurement of flow through grafts is particularly important in occasional instances in which there may be good arterial pulsation but poor flow.[53–55] Palpation of the arterial pulsation consequently may be misleading.[53–55] If the level of flow is low through a reconstructed vessel or graft, quantification of flow after direct injection of a vasodilator may enable one to distinguish between an anatomic hindrance to flow and vasoconstriction.[56] If there is a vascular occlusion, flow will not increase significantly; whereas if there is vasoconstriction, flow should increase markedly (100 to 300 percent in the femoral-popliteal region).[57] Continuous measurements of flow in shunts during reconstructive procedures of arteries to vital organs, such as the carotid artery, have decreased the risks of dangerous variations of flow in such extravascular shunts.[57]

Continuous monitoring of cardiac output during thoracic surgery by means of a flow transducer on the ascending aorta has provided valuable information to the surgeon and anesthesiologist.[53] Flow transducers have been applied about the pulmonary artery and aorta of children during surgery for ventricular septal defect and pulmonary hypertension to quantitate the left to right shunt and determine if corrective or palliative surgery is indicated.[5] Aortic flow also has been measured at surgery to quantitate the result of plastic repair of the aortic valve in patients with aortic insufficiency.[5] Backflow can readily be measured with such techniques by integration of the diastolic portion of the flow curve. Similarly, flow in the superior vena cava has been used to quantitate tricuspid regurgitation.[58]

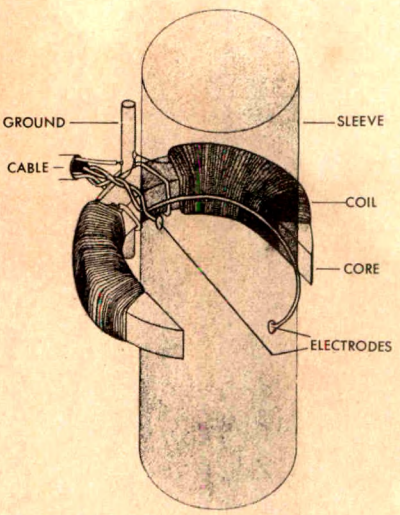


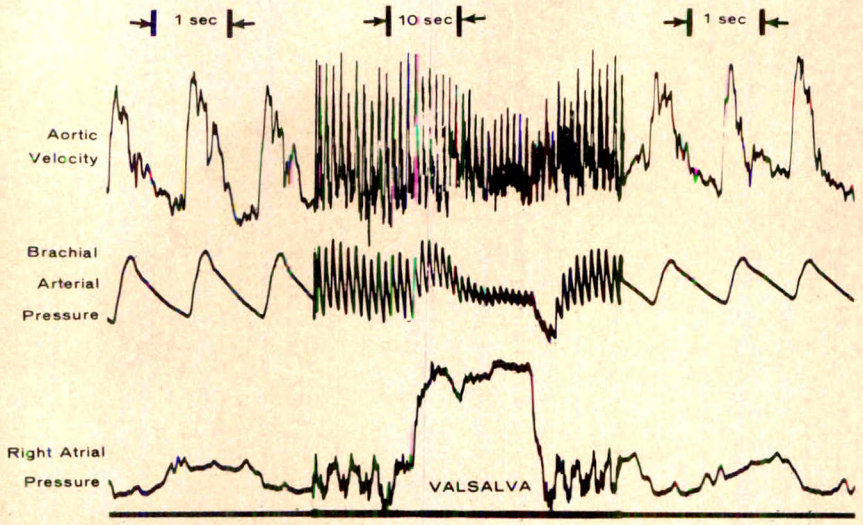
Figure 2. Schematic diagram of flow transducer showing general construction. Axis of electrodes is at right angles to field produced by electromagnet (coil and core). (Reprinted by permission from Khouri and Gregg.[29])

Studies of bypass venous grafts in the thigh have been performed from the time of operation to as long as 4 days postoperatively to quantitate flow in the graft and the effects of pharmacologic agents.[59] In most vessels, long-term measurements of flow have not been feasible because of the necessity of further surgery to remove the transducer. However, prototype versions of a cuff transducer that can be removed by traction on the protruding end have been successfully tested in animals.[60] The transducer consists of twin coiled electromagnets with a pliable core enclosed in a flexible silastic molding.

Electromagnetic perivascular transducers have several advantages: (1) Velocity and flow, averaged across the cross section, can be measured instantly and continuously; (2) there is little if any interference with flow; (3) both forward and reverse flow can be sensed; (4) calibration is linear; (5) frequency response is high; and (6) the transducers are reliable, simple and rugged. A prominent disadvantage is the necessity of surgical exposure of the vessel on which the transducer is to be placed. The method is therefore most applicable to animals, and to patients during surgery.

Catheter-Tip Techniques

Velocity sensors: To eliminate the necessity of surgical exposure of the vessels, a variety of cathe-



Ao Peak Velocity (cm/sec)	48	45	27	45
BA Pressure (mmHg)	130/90	140/110	110/100	130/100
RA Mean Pressure (mmHg)	8	45	45	8
Heart Rate (beat/min)	60	72	72	64

Figure 3. Effect of Valsalva maneuver on central aortic (A_o) velocity (**top**), brachial arterial (BA) pressure (**middle**) and right atrial (RA) pressure (**bottom**). Velocity was measured with catheter-tip transducer. During Valsalva maneuver, peak aortic velocity decreased concordantly with arterial pressure. Patient had coronary heart disease with increased left ventricular end-diastolic pressure of 21 mm Hg.

ter-tip techniques have been developed. Utilization of catheter-tip sensors is not new. The first measurement of phasic changes of blood flow by Frank[61] in 1899 was accomplished by a catheter-tip device. Modifications of the design and size of electromagnetic transducers now have made it possible to apply electromagnetic transducers to the tip of a cardiac catheter.[62–68] In general, such instruments are capable of measuring velocity in large vessels[59–64] or volume flow in specified vessels.[66,67] Some catheter-tip devices can measure both.[65,68] Electromagnetic catheter-tip velocity "probes" have many of the general advantages of all electromagnetic induction techniques and, in addition, have the major advantage of not requiring surgical exposure of the vessel in which velocity is being studied. Phasic velocity can be measured instantly and continuously in both a forward and reverse direction. Since most velocity transducers are as large as the cross-sectional area of a no. 7 catheter (diameter 2.3 mm), they are most suited for measurement of velocity in vessels of considerably greater size in order to avoid inaccuracies due to impingement upon flow by the intraluminal device itself.

The distinction between catheter-tip *velocity* transducers and catheter-tip *flow* transducers must be emphasized. Velocity is the ratio of flow to cross-sectional area. Changes in blood velocity are related to changes in flow only if the cross-sectional area of the vessel remains constant. Divergent changes between velocity and flow could occur if the diameter of the vessel changed. Velocity sensors consequently can be utilized as indicators of changes of flow only if studies of the particular intervention indicate that the cross section of the vessel is not affected by the intervention. For example, coronary sinus blood velocity was shown to vary linearly with left circumflex coronary arterial blood flow in dogs during hypoxia and the administration of sympathomimetic drugs; however, linear changes were not demonstrated after the administration of nitroglycerin.[69]

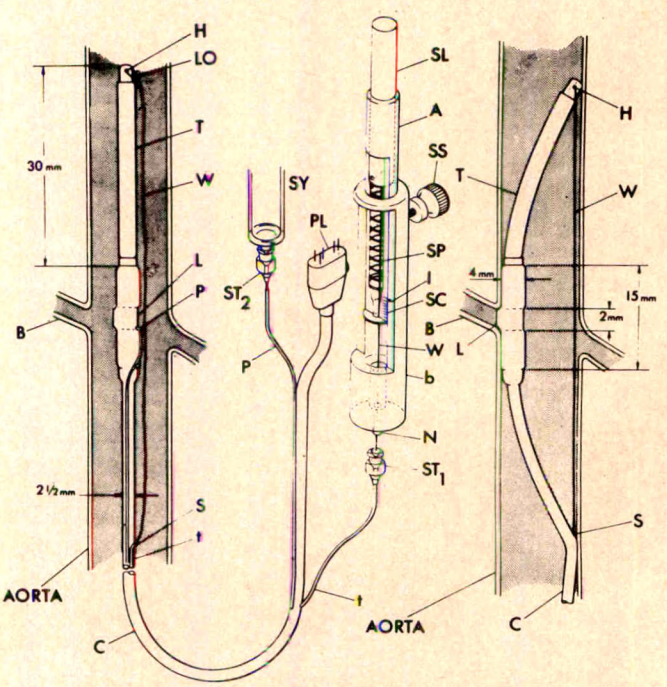


Figure 4. Catheter flowmeter. At **left,** catheter is unarched; at **right,** it is arched by tension applied to wire, W, to make crater on left side of flow transducer snap into ostium of artery branch, B. **Center,** drawing shows device for application of wire tension. (Reprinted by permission of the American Heart Association, Inc. from Kolin et al.[67])

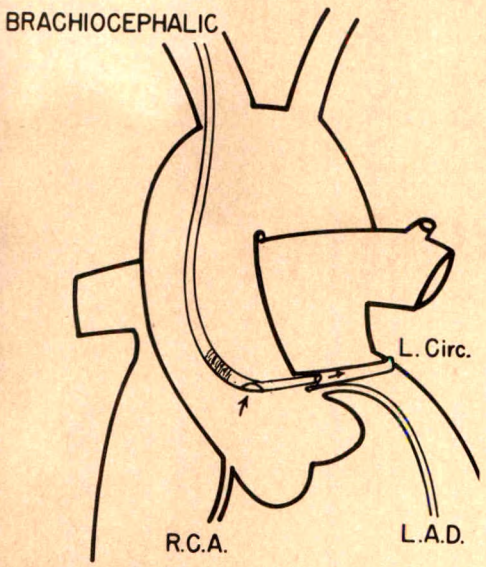


Figure 5. Diagrammatic representation of method by which catheter-tip flowmeter has measured coronary flow. Tip of transducer was wedged in left circumflex (L. Circ.) coronary artery. (In this particular dog, the left circumflex and left anterior descending (LAD) coronary arteries branched directly from the aorta.) Blood entered the side hole (**arrow**), flowed past signal electrode within the cylinder, and exited through the end hole. Obstruction to flow can be minimized if walls of cylinder are thin. (Reprinted by permission from Stein and Schuette.[65])

In spite of these intrinsic problems, catheter-tip electromagnetic velocity transducers potentially appear to have broad applicability. Measurement of phasic velocity in the superior vena cava or aorta permits quantitation of tricuspid[70] or aortic[71] regurgitation. Under controlled conditions, velocity in the coronary sinus may be used as an indicator of changes of coronary arterial flow.[69] The pattern of superior vena caval blood velocity may help distinguish between constrictive pericarditis and cardiac tamponade.[72] The first derivative of peak aortic blood velocity may be a useful index of myocardial contractility.[73] Physiologic responses such as those associated with the Valsalva maneuver perhaps may be better understood if velocity measurements are known (Fig. 3).

Catheter-tip flow transducers: Ideally, measurement of the volume of flow in a vessel would be performed continuously, instantaneously, and without interference or major surgical intervention. Significant progress has been made in an effort to attain these goals. One approach is the measurement of velocity of flow and simultaneous measurement of the diameter of the vessel by an independent means. Devices for measuring a vessel's diameter have been designed for adaptation to the tip of a velocity-sensing catheter. One consists of calibrated extendible braces.[74] Others consist of flexible metal (radiopaque) rods[75] or a flexible metal loop[76] that can widen to the diameter of the vessel and permit measurement from plain roentgenograms. Estimation of the diameter of the vessel by arteriography has also been used satisfactorily for the calculation of total flow.[77] These methods, with the exception of the latter, have not been reported in clinical studies.

Another approach to catheter-tip volume flow measurements is the employment of a fixed orifice on the catheter through which the entire flow to a vessel is caused to pass. Such devices usually have been designed for measurement of volume flow in specific vessels. One such catheter-tip transducer causes all flow to pass through a cylindrical tip at the end of the catheter by distension of a balloon around the cylinder.[66] This method gave satisfactory results in measurement of coronary sinus flow in dogs.[66] Subsequently, another catheter suited for measurement of flow in the renal or mesenteric arteries was developed.[67] This device functioned by causing the side of the catheter to lodge against the orifice of the artery; flow passed transversely through a transducer located in the body of the catheter and then into the artery (Fig. 4). The instrument, designed for measurement of flow in vessels that branch at nearly right angles from the aorta, would not be appropriate for other vessels. Total flow in vessels that branch at more acute angles from the aorta, especially the coronary arteries, has been measured by wedging a thin wall cylindrical tip of the catheter into the vessel; the main body of the catheter remains in the aorta[65] (Fig. 5). Obstruction to flow can be minimized if the walls of the cylinder are thin. The concept of a cylindrical tip of a catheter flow-sensing device wedged within a coronary artery previously has been used successfully in dogs.[78] The method has

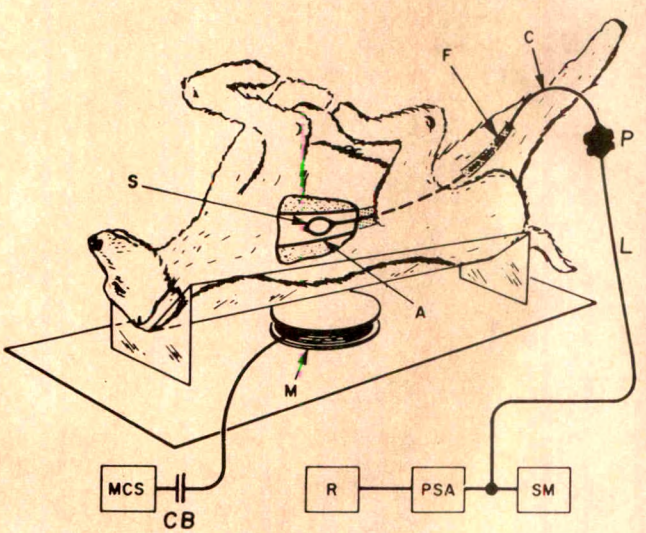


Figure 6. Scheme of external field electromagnetic catheter blood flowmeter. A = aorta (for better visualization of sensor, the heart is omitted and the artery is greatly exaggerated in size). S = sensor portion of catheter (under optimal conditions, the plane of the loop of S is parallel to the plane of the magnet coil). M = magnetic coil. (Reprinted by permission from Kolin.[68])

not yet been utilized for measurement of coronary flow in patients because of technical problems related to the fabrication of a thin, flexible, manipulatable tip. An electromagnetic flow sensor mounted on a flexible frame which collapses as it passes through a small branch vessel and expands to the diameter of the main vascular trunk has been described which is capable of measuring volume flow in branch vessels as well as the major vessels.[68,76] In contradistinction to other electromagnetic catheter-tip flow sensors, the magnetic field with this device is provided by a large electromagnet placed external to the subject (Fig. 6).

Conclusion

In 35 years, electromagnetic flowmetry has progressed to a practical and available tool. Now, diagnostic as well as physiologic studies are being performed with the technique, and other potential applications to patient care are being explored. Electromagnetic flowmeters are being utilized particularly during cardiac catheterization and cardiovascular surgery. Quantitation of blood flow by electromagnetic techniques has already contributed to the management of patients in a variety of circumstances.

Acknowledgment

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Asymptomatic Rapid Ectopic Tachycardia Induced by and Persisting During Prolonged Exertion

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A case is reported of a 39 year old healthy man who has a prolonged and unusual tachycardia, probably ventricular or atrioventricular junctional with aberration, with a rate of 214/min, during strenuous exertion in the upright position. This arrhythmia occurs whenever the exertion produced is vigorous enough to evoke a sinus tachycardia of 180/min and persists until the exertion is decreased and the sinus rate decreases below 180/min. The patient is free of cardiac symptoms both at rest and while running several miles daily during which time the unusual tachycardia is almost constantly present. There are no significant S–T segment changes during or after exercise.

Paroxysmal ventricular tachycardia has been reported in persons with otherwise normal hearts[1–11] and may produce no symptoms if the attack is brief and occurs at rest; but symptoms, frequently incapacitating, occur if the attack is prolonged and initiated by physical activity. This report concerns a man who invariably experiences an unusual tachycardia, probably ventricular or atrioventricular (A–V) junctional with aberration, during vigorous exertion without untoward symptoms and, indeed, feels refreshed afterward, even though the ventricular rate during exertion may be as high as 214/min and the arrhythmia persists as long as vigorous activity is maintained (18 to 30 minutes).

Case History

The subject is a 39 year old man who was referred to one of us because his electrocardiogram disclosed occasional premature ventricular complexes and minor T wave inversions in the lateral precordial leads. He was free of cardiac symptoms and ran several miles each morning without any difficulty. The family history revealed no heart disease.

Physical examination and X-ray study of the chest were normal. The initial electrocardiogram (Fig. 1) revealed flattened T waves in the limb leads with slight terminal inversions in the lateral precordial leads V_5 and V_6. Results of a 2-step Master's exercise test were negative, and the exercise produced neither fatigue nor dyspnea. However, occasional premature ventricular contractions were noted singly or in sequence (Fig. 1).

A Holter apparatus[12] was used to monitor the patient's electrocardiogram (Avionics Research Products Corp.), during a typical 10 hour period and particularly during his running period in the morning. Again, no symptoms were revealed. Prior to his running, the electrocardiogram again displayed occasional premature ventricular complexes. During exertion, the ectopic beats increased in frequency and occurred in sequence as the normal sinus rate increased from 110 to 170/min. When the sinus rate reached 180/min a rapid and slightly irregular arrhythmia appeared at a rate of 214/min and persisted throughout the remainder of the running period, approximately 18 minutes. This ar-

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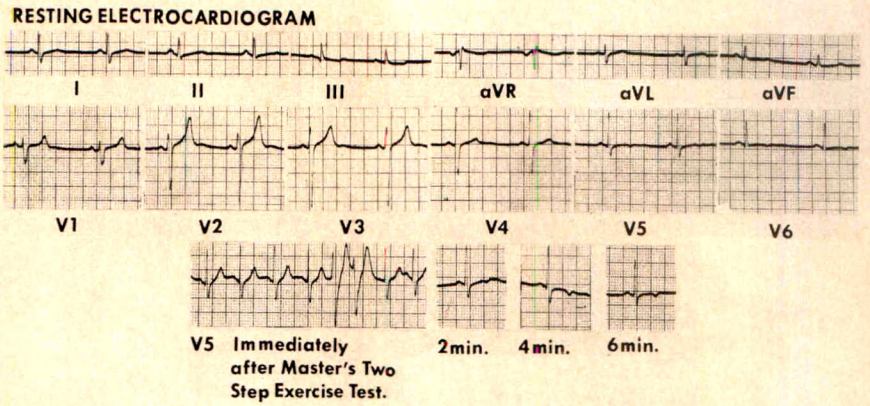

Figure 1. Initial resting electrocardiogram (**above**) and after Master's exercise test (**below**). Note the 2 successive premature ventricular contractions occurring immediately after exercise and the nonspecific T wave abnormality that appears before and after exertion.

rhythmia was interpreted as ventricular tachycardia with occasional ventricular capture beats (Fig. 2). Normal sinus tachycardia at a rate slightly less than 180/min appeared immediately after running, interrupted by recurrent premature contractions, occasionally in sequence, and short runs of the tachycardia.

In an attempt to delineate the precise mechanism of the arrhythmia, he walked on a treadmill successively for 1 minute at a rate of 2, 3 and 4 miles/hour and then at 5 miles/hour at a 5° incline for 15 minutes. The ectopic tachycardia of 214/min reappeared, preceded and followed by a sinus tachycardia with a maximal rate of 180/min without alteration of the S–T segment (Fig. 3).

The patient was further studied in the following manner: A bipolar electrode catheter was inserted into the left antebrachial vein after proper surgical preparation, and the catheter advanced into the superior portion of the right atrium. An intraatrial electrocardiogram and simultaneous lead V_5 were recorded during supine exercise using a bicycle ergometer for 15 minutes at the highest work load, 2,800 ft lb/min. Occasional ectopic ventricular beats occurred, but not nearly as frequently as noted during upright exercise (Fig. 4). However, the sinus rate never surpassed 110/min during supine exercise.

The bipolar electrode was next used as a right atrial pacemaker, stimulating the right atrium near the junction of the atrium and the superior vena cava. However, the atrium could not be paced at a rate greater than 125/min without some degree of A–V block occurring, thus again preventing the rapid rate which seemingly was necessary as a prelude to the appearance of the ectopic tachycardia.

Finally, with the catheter fixed in place at the antebrachium so that the electrode would remain at the high right atrium level, the patient was allowed to stand and then to exercise on the treadmill at the same rate and incline as had been done previously. The right atrial electrocardiogram and simultaneous lead V_5 were recorded continuously and when the sinus tachycardia reached a rate close to 180/min the ventricular premature beats became more frequent and were then replaced by long runs of the ectopic tachycardia, again without producing symptoms (Fig. 5 and 6).

Discussion

Because high grade sinus tachycardia with subsequent development of the ectopic tachycardia could not be produced by vigorous exercise in the supine position, it was not possible to obtain His bundle recordings during the ectopic tachycardia.

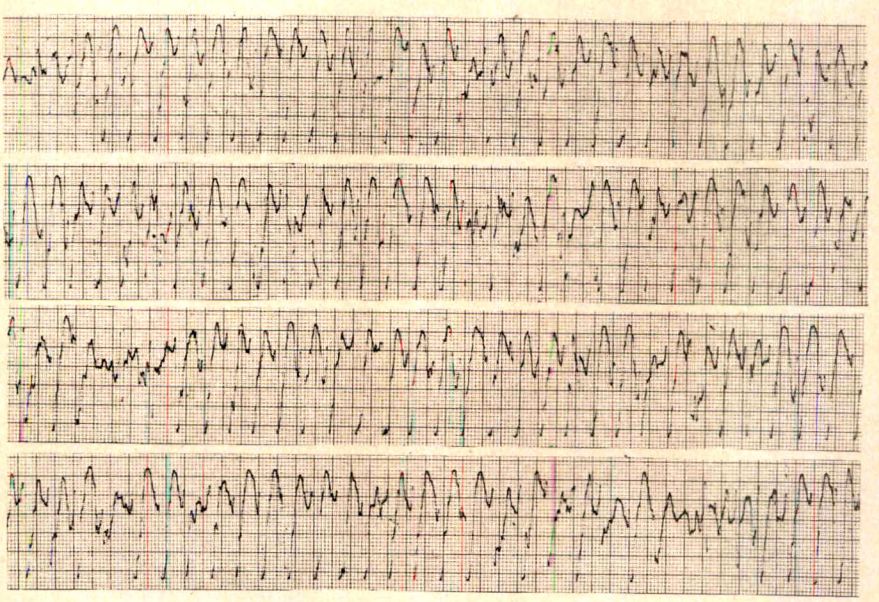

Figure 2. Continuous rhythm strip (37 seconds) representative of the arrhythmia which was present for 18 minutes during strenuous exertion. There is an ectopic tachycardia, rate 214/min, with occasional ventricular capture.

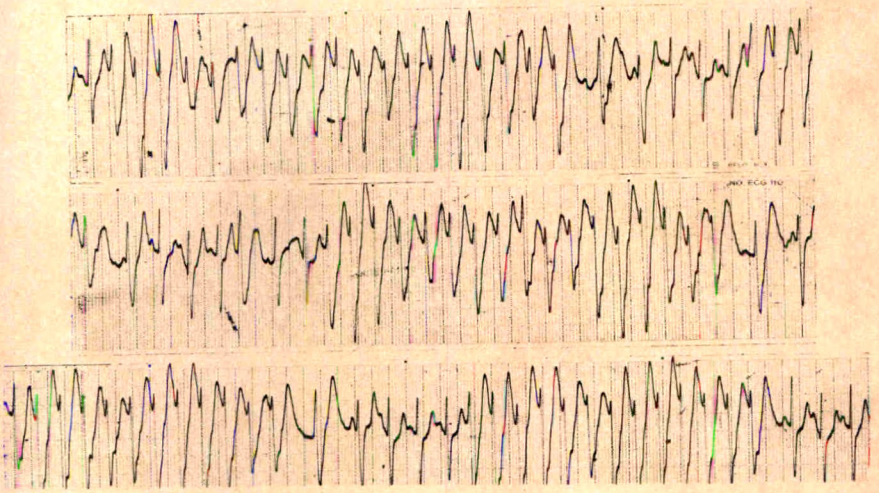

Figure 3. Representative rhythm strips recorded during treadmill exercise showing paroxysmal tachycardia with occasional ventricular capture at a sinus rate of 175 to 180/min. Note the compensatory pause between the ectopic arrhythmia and ventricular captures.

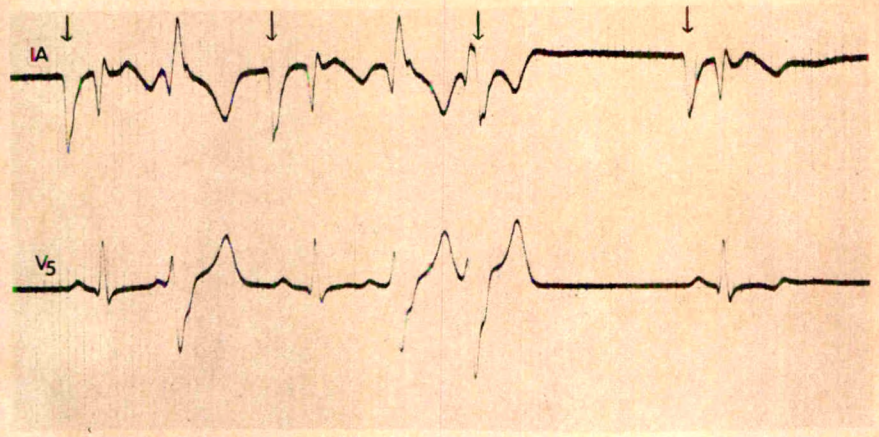

Figure 4. Simultaneous intraatrial and V_5 electrocardiogram. **Arrows** denote atrial depolarization. Note that the direction of the initial deflection of ectopic QRS complexes in lead V_5 is opposite to that of the initial deflection of the normally conducted QRS complex. Also note the presence of 2 ectopic beats occurring in succession between 2 normally depolarized atrial complexes, as well as the compensatory pauses following the ectopic complexes.

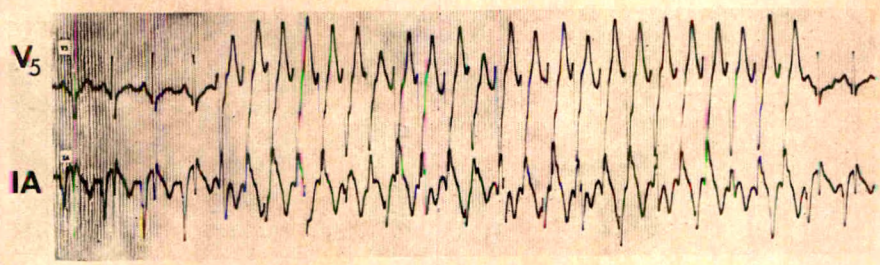

Figure 5. Simultaneous intraatrial and lead V_5 electrocardiogram during treadmill exercise. Paroxysmal ectopic tachycardia, ventricular or A–V junctional with aberration in origin. Note the independent atrial and ventricular depolarization and compensatory pause following the last ectopic beat of the series.

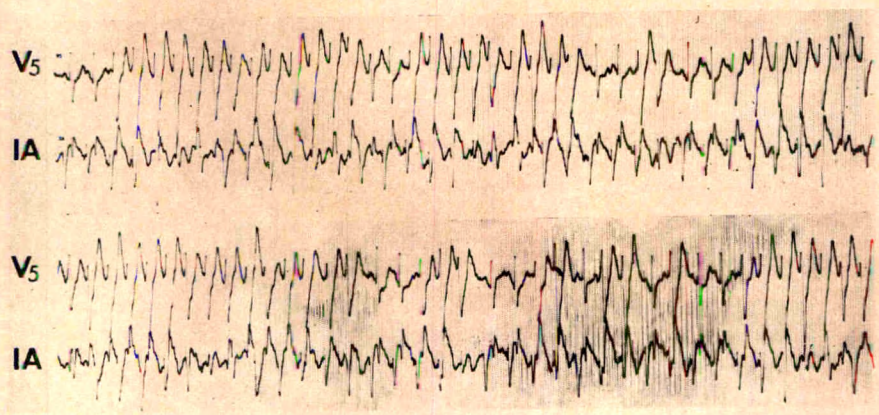

Figure 6. Two representative strips showing ectopic tachycardia during treadmill exercise. Simultaneous lead V_5 (**above**) and intraatrial lead (**below**) in each strip. Note the independent atrial and ventricular depolarization.

For this reason, a precise mechanism of the tachycardia is open to question. However, there are many features that strongly favor the diagnosis of ventricular tachycardia.

The presence of numerous premature ventricular complexes, frequently in succession, the initiation of the tachycardia with an abnormal ventricular complex, the close resemblance between the configuration of the isolated premature ventricular complexes and those present in the ectopic tachycardia, compensatory pauses between the last ectopic QRS complex of the tachycardia and the subsequent normal sinus conducted ventricular complex, the presence of slight variations in the QRS complexes which could be due to superimposed P waves or possible fusion beats, and the independent atrial complexes noted on intraatrial electrocardiogram, all suggested the diagnosis of ventricular tachycardia. In addition, the initial deflection of the premature ventricular complexes in lead V_5 is opposite in direction to that of the normally conducted beat, a finding also favoring the diagnosis of ventricular tachycardia. Nonetheless, we acknowledge that a definitive diagnosis of the arrhythmia cannot be made without His bundle recordings. Easley and Goldstein[13] have reported the use of competitive atrial pacing as an aid in differentiating ventricular tachycardia from junctional tachycardia with aberrant conduction, but that technique did not help us since we were not able to pace the atria at a faster rate than 125/min.

Although paroxysmal ventricular tachycardia occurs most commonly in the presence of serious heart disease, in a substantial number of cases, approximately 10 to 12 percent in some of the larger series,[5,6] no apparent heart disease is present. In some of the reported cases,[2,5,8-10] as in ours, the onset of the paroxysm of ventricular tachycardia was clearly related to exercise and the attainment of a rapid sinus tachycardia. Our patient is of exceptional interest because he had no symptoms, despite the exceptionally rapid rate, the strenuous exertion and the long duration of the arrhythmia. Completion of exercise was never induced by symptoms but was related only to the completion of the chore or task which the patient had set out to do.

Our patient offers a therapeutic dilemma. By his own admission, he has never felt better or ever been in better physical condition. Decreasing his morning exercise made him unhappy, "sluggish and irritable." If it is possible that cessation of exercise could decrease the efficiency of skeletal muscle metabolism previously conditioned by the exercise, then the onset of a future paroxysm of the ectopic tachycardia due to a sudden, unaccustomed exertion might conceivably result in serious symptoms.

There is a correlation between the presence of ectopic ventricular beats in asymptomatic persons and the presence of coronary heart disease,[14,15] and our patient has shown minor T wave change in the resting electrocardiogram. Nevertheless, his ability to undergo strenuous exertion with no symptoms, with an ectopic tachycardia of 214/min and without significant changes in the S–T segment during rapid sinus tachycardia or after exertion, argues against the presence of underlying heart disease, particularly coronary artery disease.

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Congenital Complete Atrioventricular Heart Block

A 25 Year Follow-Up Study

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A man with congenital complete heart block has been followed up for 25 years to age 48. His progress, present clinical condition and response to exercise, are described. The study emphasizes the excellent prognosis in congenital complete heart block, provided there is no associated congenital structural heart disease, the QRS complexes are supraventricular in configuration, and the condition is not familial.

A unique opportunity to review the natural history of congenital complete heart block over a period of 25 years in a trained pilot now aged 48 years prompted this communication. Because the prognosis in congenital complete heart block differs strikingly from that in acquired heart block,[1–9] awareness of the natural history and criteria for the clinical diagnosis of congenital complete heart block is essential. The following case is presented to provide further information on the natural history of congenital complete heart block, as well as to discuss the clinical diagnosis and response to exercise in this condition.

Case Presentation

The patient, who is now a 48 year old man, has been under periodic study by one of us since 1945 because of complete heart block. He was 1 of 3 normal children; his 2 sisters are alive and well and have normal electrocardiograms. His mother, aged 72 years, has a normal electrocardiogram. His father died at age 68 years of leukemia; no electrocardiograms were available. There is no history of rheumatic fever or other infectious disease known to be associated with heart block. The patient enjoyed an active childhood. His mother first became aware of his slow pulse when he was 10 years old.

In 1941, at age 19 years, he was considered medically fit for aircrew duties with the Royal Canadian Air Force (R.C.A.F.). The heart rate documented during his first 4 years of service ranged from 46 to 56 beats/min. On examination in 1945 at age 23 years, his height was 66 inches and weight 139 lb; heart rate was 48/min and blood pressure 130/68 mm Hg. There was a faint systolic murmur at the apex which varied with respiration. In the supine position, a pulmonary systolic murmur was also heard. Chest roentgenogram revealed normal heart size and contour. Electrocardiogram showed complete heart block (Fig. 1). Following exercise, 50 minutes after subcutaneous injection of atropine, 0.02 grain, the ventricular rate was 60/min; the atrial rate, which was 83/min at rest, increased to 115/min. The subject was exposed to a simulated altitude at 22,000 feet in a standard R.C.A.F. decompression chamber and exhibited a normal response. He also showed a normal tolerance for gravity.[10] In 1952 he began to fly jet aircraft and subsequently completed an advanced jet fighter course. At age 33 years it was ruled that he be removed from combat flying, and for the past 15 years he has been engaged in nonflying activities. However, he leads an active life and participates in competitive sports without cardiovascular

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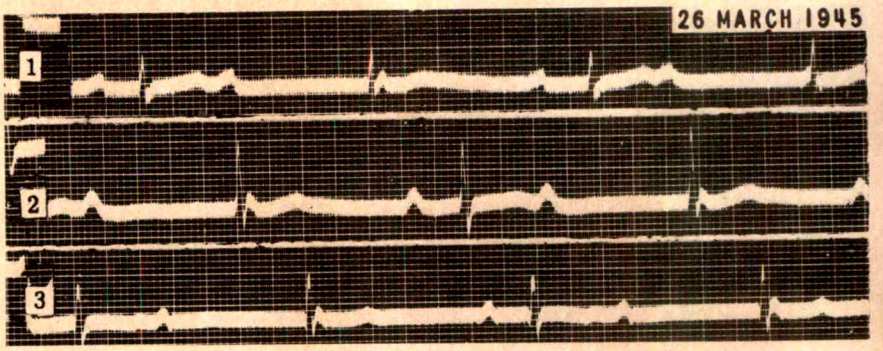

Figure 1. Resting electrocardiogram in 1945 showing complete heart block. Atrial rate is 74, ventricular rate 44/min.

symptoms. In 1963, he underwent a submucous resection under general anesthesia, and at a later date a hemorrhoidectomy; both procedures were uneventful.

When examined on June 15, 1970 at age 48, he categorically denied syncopal episodes, dizziness, weakness, angina, dyspnea or palpitation. He was receiving no medication. Height was 66 inches, weight 152 pounds, blood pressure 150/86 mm Hg in right and left arms, and pulse 52 regular and of full volume. Inspection of the internal jugular veins revealed *A* waves at a rate of 70/min and occasional cannon *A* waves. The apex beat was palpable in the fifth interspace 10.5 cm. lateral to mid-line. There were no thrills. The first heart sound varied in intensity; the second heart sound was normal. A grade 2/6 systolic ejection murmur was present at the second left interspace at the costal margin; the murmur decreased when the patient was examined in the sitting position and was accentuated immediately after exercise. The liver was not palpable. All peripheral pulses were full and symmetrical. The electrocardiogram showed complete heart block (Fig. 2). The ventricular rate was 52/min, and the QRS complexes were supraventricular in type. Chest roentgenogram (Fig. 3) revealed a normal cardiac silhouette and normal pulmonary vasculature.

On June 16, 1970 the patient performed a progressive exercise test using the bicycle ergometer, with continuous electrocardiographic monitoring. The work load was gradually increased to 900 kilopondmeters, and the atrial and ventricular rates increased (Table I). Continuous electrocardiographic monitoring during and after exercise showed that complete atrioventricular (A–V) block persisted throughout. No angina, weakness or syncopal episodes were present.

Discussion

The survival rate in complete heart block is largely dependent on etiologic factors. In contrast to acquired complete heart block, the prognosis in congenital complete heart block is excellent, provided there is no associated congenital structural heart disease, the QRS complexes are supraventricular in configuration, and the condition is not familial.[1–9] Campbell and Emanuel[2] followed up 5 patients with congenital complete heart block without associated structural anomalies for 34 to 40 years; the patients were between 47 and 67 years of age at the time of their report. In 1, essential hypertension had developed; the remaining 4 were leading normal active lives. The only patient to experience Stokes-Adams attacks had them frequently in infancy, but only occasionally later on. In another, complete heart block changed to first degree heart block betwen the ages of 35 and 42 years, and for the last 12 years of observation the

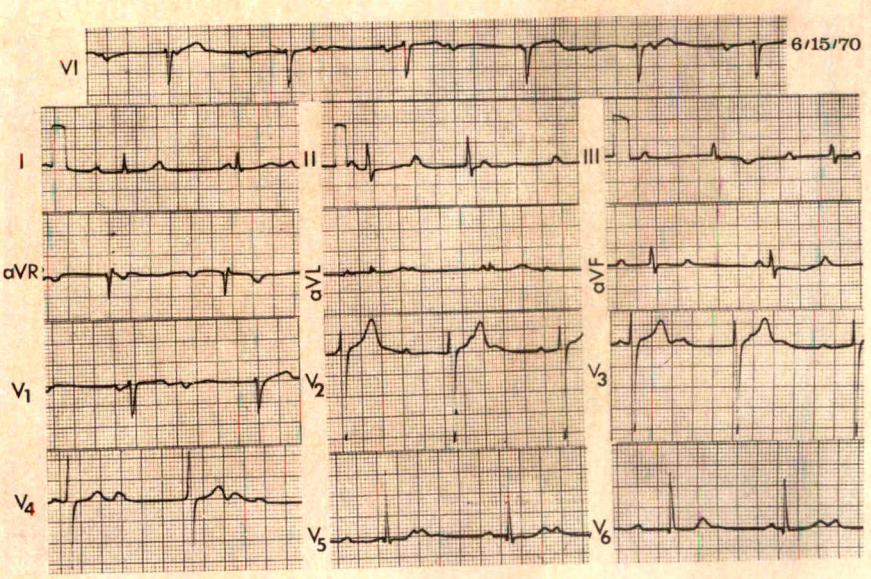

Figure 2. Resting electrocardiogram in 1970 showing complete heart block. Atrial rate is 96, ventricular rate 52/min.

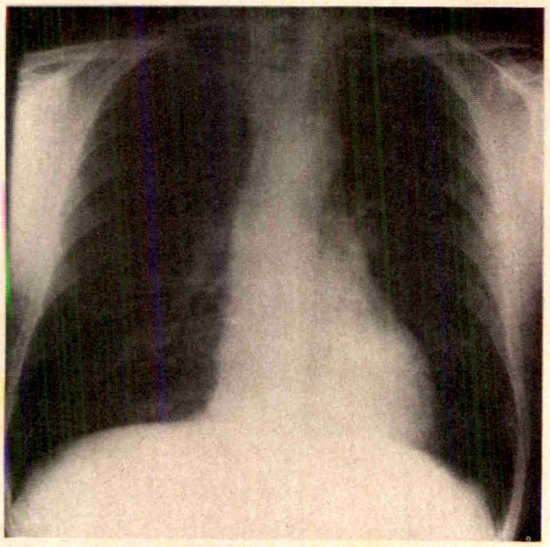

Figure 3. Chest roentgenogram in 1970. The heart shadow is normal in size; cardiothoracic rate is 14.0/32.5 cm.

subject had not had complete heart block. Benjamin and White[4] reported on 2 women each known to have complete heart block for 35 years. One was aged 58 and fully active at the time of their report; the second patient died suddenly at age 57 years, and Lev et al.[11] have reported the results of the histopathologic study of the conductive system. This patient had experienced episodes of atrial flutter with a high grade A–V block. Nakamura and Nadas[5] reviewed the medical records of the Children's Hospital Medical Center in Boston between 1938 and 1963. They were certain no associated congenital heart disease was present in 11 of the 61 patients reported; 1 of the 11 died of a Stokes-Adams attack during the followup period, which averaged 8½ years.

Criteria for diagnosis: The criteria established by Yater[12] for the diagnosis of congenital heart block were: (1) A–V block proved by graphic methods in young persons; (2) bradycardia noted at an early age; (3) absence of a history of infectious disease such as diphtheria, rheumatism or syphilis, which may be responsible for postnatal heart block; and (4) the presence of congenital heart disease or syncopal attacks, or both, during childhood. Campbell and associates[1,2] have challenged the concept that associated congenital cardiac malformations are essential for the diagnosis of congenital heart block. Several studies[5,7,13,14] of patients with congenital complete heart block have established that no associated congenital cardiac malformations need be present. Although Stokes-Adams attacks are more frequent in patients with congenital complete heart block who have wide QRS complexes and relatively slow ventricular rate,[3,6,8,9] they have been reported in patients with congenital complete heart block whose QRS complexes are supraventricular in configuration.[2,5]

TABLE I

Results of Progressive Exercise Test

Condition	Time (min)	Atrial Rate (beat/min)	Ventricular Rate (beat/min)	Blood Pressure (mm Hg)
Rest	0	70	45	165/90
300 kpm	3	100	78	210/100
600 kpm	3	128	96	200/110
900 kpm	2	155	110	210/110
Recovery	1	112	64	...
Recovery	3	110	50	165/88
Recovery	5	96	48	...

kpm = kilopondmeters.

Response to exercise: Most patients with congenital complete heart block without associated structural cardiac malformation lead normal and active lives.[2,4,5,10] The normal response to exercise involves an integrated adjustment of heart rate and stroke volume. Ikkos and Hanson[15] described the hemodynamic and electrocardiographic response to graded exercise in 11 patients with congenital complete A–V block. During exercise, all patients showed increases in both atrial and ventricular rates. The ventricular rate observed during exercise ranged between 68 and 130/min. No correlations were found between increases in ventricular rate during exercise and resting rate, atrial rate or heart size. The atrial rate during exercise increases almost stepwise with increasing working loads, but a stepwise increase in ventricular rate was found in only a few cases. In their review of the hemodynamics of congenital heart block, Scarpelli and Rudolph[16] pointed out that the effects of sympathetic activity are considerably more pronounced than those of parasympathetic activity. Although exercise generally resulted in a significant increase in ventricular rate in patients with congenital heart block, it is unusual for the ventricular rate to exceed 100 to 130/min.[5,6,13,15,16] The cardiac output in congenital heart block is usually normal despite a reduction in ventricular rate; this is accomplished by an increased stroke volume.[16]

Diagnosis in present case: In 1956 Mathewson and Harvie[10] first reported on the patient with congenital complete heart block described herein; he had then been followed up for 10 years. He has now been followed up for 25 years to age 48 and throughout this long period of observation has remained asymptomatic and fully active. He has no clinical or radiographic evidence of an associated congenital cardiac abnormality, and has never experienced a Stokes-Adams attack. There is no history of infectious disease, either in the mother during pregnancy or in the patient during infancy and childhood, known to be associated with the development of heart block. The QRS complexes are supraventricular in type, and the ventricular rate

is approximately 50/min; these electrocardiographic findings support the statement that the heart block in this patient is congenital.[1,3,7,8,13] A slow pulse was noted by the mother when he was 10 years old, and electrocardiographic documentation was provided when he was 19 years old. Although unequivocal evidence for the congenital nature of complete heart block requires that the diagnosis be made before or shortly after birth, the presence of a slow pulse in childhood, the absence of associated structural heart disease or Stokes-Adams attacks, and the subsequent electrocardiographic evidence of complete heart block with a relatively rapid ventricular rate and supraventricular QRS configuration, justify the diagnosis of congenital complete heart block in this case.

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Factors Influencing Longevity in Adults with Congenital Complete Heart Block

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Congenital complete heart block in adults is uncommon. The incidence of associated congenital heart disease is low and life expectancy is reported to be normal. Eight patients with this disturbance of conduction but without heart disease are described. Five experienced Adams-Stokes syncope. Three required permanent pacemakers, 2 because of potentially lethal arrhythmias and 1 because of decreasing cardiac output associated with deceleration of the basic junctional pacemaker. An additional 2 patients required temporary pacing because of Adams-Stokes episodes near term pregnancy. A possible mechanism for the arrhythmias and clinical deterioration is considered. Although longevity of these patients is not denied, it is apparent that complications may develop unpredictably throughout their lifetime.

Pathologic studies now suggest that in many instances congenital complete heart block may represent an anatomic separation of conduction fibers in the central fibrous body of the heart[1] causing interruption of impulses through the atrioventricular (A–V) node. In a small number of patients His bundle recordings have identified that the dominant pacemaker arises in junctional tissue either near the A–V node or in the bundle of His[2,3] and an electrocardiogram typical of congenital complete heart block has been produced by pacing of the bundle of His.[3]

In spite of the failure of sequential A–V conduction, many reports have documented prolonged survival of patients. Campbell and Emmanuel[4] followed up 6 adult patients for 34 to 40 years. Five had an uncomplicated course, and only 1 had Adams-Stokes attacks. These occurred intermittently over a period of 48 years with as much as 19 years separating individual episodes. Patients surviving into the sixth and seventh decades have been described.[5,6] Normal physical working capacity with strenuous exercise testing has been reported by Mathewson and Harvie.[7] A patient cited by Gazes et al.[8] tolerated 6 deliveries without hemodynamic or electrical deterioration. The mechanism of death in adult patients with congenital complete heart block has seldom been documented.[9]

The longevity of adult patients is assumed to be due to several causes: (1) the presence of an accelerated junctional pacemaker site under autonomic control; (2) the stability of this pacemaker without the emergence of idioventricular foci; (3) continued and appropriate hemodynamic responses to stress and exercise; and (4) the infrequency of congenital heart disease.

This report describes 8 adults with assumed congenital complete heart block but without congenital or acquired cardiovascular disease (Table I). Only 3 subjects were without important

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TABLE I

Clinical Summaries of 8 Adults with Congenital Complete Heart Block

Case no.	Age (yr) & Sex	Age at Diagnosis* (yr)	Heart Rate (beats/min) A	Heart Rate (beats/min) V	QRS Duration (sec)	Syncope	Low Output	Electrocardiographic Features	Comment
1	52F	28	80 73	68 34†	0.08	+	—	Progressive slowing of ventricular rate; ventricular fibrillation	Psychotic; temporary pacing at time of surgery to remove abdominal hemangiopericytoma; permanent pacing subsequent to spontaneous ventricular fibrillation
2	44F	7	86	38†	0.08	+	+	Progressive slowing of ventricular rate	Permanent synchronous pacing for low cardiac output symptoms
3	43F	4	67	42†	0.08	+	—	Mechanism of syncope not documented	Permanent pacing (fixed-rate, later synchronous) for recurrent Adams-Stokes syncope
4	35F	2	72	57	0.07	—	—	...	Two normal deliveries; asymptomatic
5	31F	3	84	62	0.08	—	—	...	Successful delivery; asymptomatic
6	29F	1	79	68†	0.08	+	—	Ventricular asystole at term; ventricular tachycardia with exercise	Temporary transvenous pacing at term
7	28F	6	64 75	42† 68	0.08	+	—	Profound bradycardia at 30th week of gestation	Prophylactic transvenous pacing at term
8	20M	Inf.	85	73	0.07	—	—	...	Asymptomatic

* By typical electrocardiogram or first record of persistent bradycardia.
† Rate before pacing.
A = atrial; inf. = infancy; V = ventricular.

symptoms. Although congenital heart block is admittedly consistent with long life, it clearly is not a benign condition and may at times rival acquired heart block in the severity of complications.

Description of the Sample

A number of conditions must be fulfilled before a diagnosis of congenital heart block without structural heart disease can be made, since in adult patients fibrosis of the conduction system can occur at any age[10] and this and other influences may mimic congenital block. In this group of 8 patients cardiac medication, heart surgery and inflammatory myocarditis were first excluded as causes. Second, structural heart disease was ruled out by cardiac catheterization in 4 patients and ruled out clinically in the remainder on the basis of a normal chest roentgenogram and normal cardiac findings on physical examination. Third, in all subjects the electrocardiogram showed complete A–V dissociation without evidence of capture by sinus impulses, an accelerated junctional pacemaker producing normal-appearing QRS complexes at rates from 45 to 80/min at rest and increasing with effort and administration of amyl nitrite. Fourth, in 4 patients the diagnosis was confirmed by electrocardiograms recorded in infancy or within the first 2 years of life. In the other 4 the diagnosis was presumed because of a long history of bradycardia and typical electrocardiographic changes.

Case Summaries

Case 1: A 52 year old schizophrenic woman was hospitalized for evaluation of a left flank mass in August 1968. Bradycardia had been identified for approximately 25 years. A routine preoperative electrocardiogram showed complete heart block, a ventricular rate of 68/min and was consistent with congenital complete heart block. The patient's history was unreliable, yet she mentioned frequent dyspnea and syncopal episodes. Right and left heart catheterization was performed and excluded intracardiac left to right shunting, corrected transposition of the great vessels and valvular disease. A temporary transvenous pacemaker was inserted and surgery performed. A large tumor identified as an hemangiopericytoma was removed. Pacing was discontinued 48 hours after operation.

Within the next 4 months the patient was twice hospitalized for surgical repair of a flank defect caused by operation and subsequent irradiation. A progressive decrease in ventricular rate was observed during electrocardiographic monitoring, but pacing was not instituted. In September 1969, the patient was readmitted because of sudden syncope. The admission electrocardiogram revealed a ventricular rate of 34/min with multifocal ectopic impulses (Fig. 1). Circulatory arrest due to ventricular fibrillation occurred 4 hours later. After emergency resuscitation, a temporary transvenous pacemaker was inserted followed by a permanent demand pacemaker system 4 days later. The patient is presently asymptomatic.

Case 2: A 41 year old woman with congenital complete heart block diagnosed at age 7 was hospitalized in November 1967. A regular ventricular rate of 50 to 70/min had been present for many years. Three episodes of Adams-Stokes seizures had occurred in the

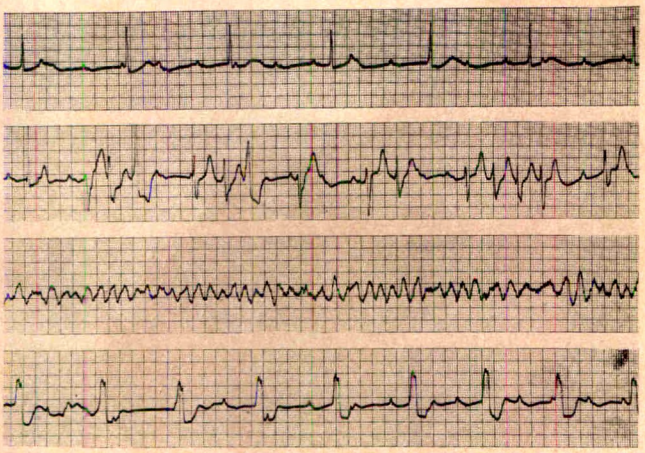

Figure 1. Case 1. Noncontinuous strips demonstrate a slow junctional rhythm (rate 34/min). Multifocal ectopic beats appear and progress to ventricular fibrillation. Administration of direct-current countershock and isoproterenol restored a faster pacemaker either one of ventricular origin or a higher one aberrantly conducted to the ventricle.

third and fourth decades, but no syncopal episodes had been recorded for 5 years before admission. However, during the 2 years before hospitalization, there had been progressive weakness, dyspnea and inability to perform comfortably physical acts previously well tolerated. Examination revealed a ventricular rate of 38/min and a soft systolic ejection murmur at the base and left sternal border. There was mild cardiac enlargement on the chest roentgenogram, and the electrocardiogram was typical of congenital complete heart block. Cardiac catheterization findings were normal at rest, but with exercise an increased arteriovenous oxygen difference and inappropriate increase in cardiac output were noted, and the heart rate increased only from 40 to 65/min with moderate effort. Since it appeared that decreased output and a slower pacemaker rate were responsible for symptoms, thoracotomy was performed and a synchronous pacemaker lead system and pulse generator were implanted. Postoperatively there has been a decrease in heart size and improvement in effort tolerance.

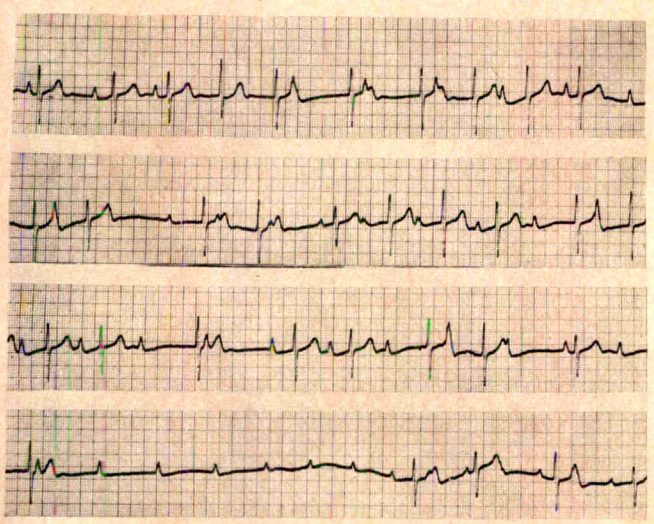

Figure 2. Case 6. A series of noncontinuous electrocardiographic strips reveal a junctional rhythm of 68/min. Its discharge rate slows intermittently, allowing a slower junctional escape at a rate of 47 to 51/min. (first, sixth and seventh complexes, **upper strip**). The rate of the escape pacemaker varies in the second and third strips but progressively slows and upon its failure ventricular asystole occurs (**bottom strip**).

Case 3: A 44 year old woman had been evaluated at age 4 years because of weakness and fatigue. Bradycardia was identified and, after an electrocardiogram was obtained, "congenital heart disease and heart block" were diagnosed. At age 21 she began to notice infrequent episodes of dizziness and lightheadedness without syncope. These disappeared for approximately 10 years, and the resting heart rate continued to be 60 to 70 beats/min. Syncope reappeared in 1961, and for almost 6 months the patient had recurrent episodes of sudden unconsciousness. Heart rates remained consistently in the range of 40/min. She was hospitalized, and chest roentgenogram and cardiac catheterization findings at rest were normal. In 1962 at age 36 years, a Hunter-Roth stainless steel electrode was implanted and was coupled to a fixed-rate pulse generator. Syncopal episodes disappeared, and the patient became asymptomatic. Fracture of 1 wire was identified by X-ray examination 2 years later, but pacing continued. In 1965, the entire pacemaker system was replaced with a synchronous electrode and pacing unit. One battery change has been required since that time. The patient is presently asymptomatic.

Case 4: A 35 year old housewife with congenital heart block diagnosed at age 2 years was referred for evaluation. She had experienced no syncope or symptoms of decreased cardiac output. Resting heart rate ranged from 55 to 65 beats/min, increasing to 110/min with treadmill exercise and to 107/min with inhalation of amyl nitrite. No change in ventricular rate occurred with administration of atropine or carotid sinus pressure. Two uneventful pregnancies have occurred in 5 years of follow-up studies, and the patient is asymptomatic.

Case 5: A 31 year old nurse was referred for consideration of permanent pacemaking. Congenital complete heart block had been diagnosed at age 3 years. Throughout her years in nursing she had carefully recorded her pulse rate, which had consistently been 60 to 75/min. No syncopal episodes had occurred, and she had a single normal delivery. On maximal treadmill effort she achieved a ventricular rate of 115/min. Her rate increased slightly with administration of atropine and significantly (102/min) with inhalation of amyl nitrite. Permanent pacing was not advised.

Case 6: A 29 year old woman with congenital complete heart block identified in her first year of life was hospitalized during the thirty-fifth week of her second pregnancy. For 2 weeks she had complained of dizziness and then experienced 2 episodes of lightheadedness followed by unconsciousness. Ventricular asystole was documented electrocardiographically (Fig. 2) and was associated with slowing and muffling of fetal heart tones. Promptly a pacing catheter was passed. Cesarian section was performed uneventfully 16 hours later. Pacing was discontinued after 24 hours. Ephedrine was prescribed in the postpartum period. Physical working

capacity was tested by treadmill exercise 3 months later. At an oxygen consumption of 2,400 cc/min and a ventricular rate of 105/min, rapid ventricular tachycardia occurred (Fig. 3) and effort was discontinued. The patient has had no further syncope, and medication has not been required. However, major emotional problems based partially on fear of subsequent cardiac arrest have required psychiatric care.

Case 7: A 28 year old housewife was found to have bradycardia (rate 30/min) at the age of 6 years. She remained asymptomatic until the thirtieth week of her first pregnancy when she began to notice dizziness on effort. Symptoms became more frequent and were followed by a series of 10 periods of unconsciousness in 7 days. Bradycardia (rate 42/min) was apparent on the resting electrocardiogram. She was given ephedrine, 50 mg every 4 hours for 2 weeks, and the syncope disappeared. She was hospitalized electively in the thirty-fifth week of gestation with a resting heart rate of 75 beats/min. A temporary transvenous pacemaker was inserted prophylactically, and pacing was initiated at a rate of 100/min. Labor was induced with pitocin, and spontaneous delivery occurred in 12 hours. Pacing was continued for 24 hours, and the catheter was removed 2 days later. Exercise testing was performed after 3 months and was normal. With ephedrine therapy, ventricular rate continues at 60 to 70/min. His bundle recordings performed 2 years later (Fig. 4) indicated a junctional pacemaker site with a constant and normal H–V interval.

Case 8: A 20 year old male college student was evaluated because of a known diagnosis of congenital complete heart block made in infancy and because of his desire to compete in intramural athletics. Chest roentgenogram, physical examination, cardiac catheterization and maximal treadmill testing showed normal findings. After 12 minutes of walking (oxygen consumption 3,400 cc/min), the ventricular rate was 123/min. No arrhythmia or QRS widening was identified. Permission was given to participate in athletics.

Discussion

The patients presented in this report represent an unusual group for several reasons: (1) Congenital complete heart block had been identified in most of them early in life, allowing prolonged clinical observation. (2) A high incidence of arrhythmias and Adams-Stokes syncope was found. (3) The frequency of temporary or permanent electrical pacing was high. (4) Studies in 4 patients suggested that the pacemaker site was low in the bundle of His and apparently not under vagal influence. (5) Only 1 criterion for longevity was met.

Because a diagnosis of congenital complete heart block had been made, most patients had been carefully followed up. Although symptoms occurred unpredictably, review of clinical records or electrocardiograms showed a progressive decrease in resting heart rate which was more marked in older patients. Syncope appeared to be due to release of lower junctional or idioventricular pacemakers as recorded in Case 1. A similar mechanism appeared

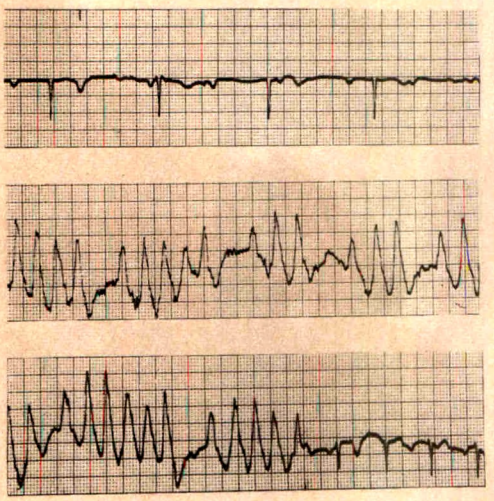

Figure 3. Case 6. Abrupt onset of ventricular tachycardia with exit block occurs at the end of treadmill effort. There was a spontaneous reversion to a junctional pacemaker. Within 10 minutes, the preexercise rate of 45/min had returned.

to be responsible for the low cardiac output state in Case 2. In congenital complete heart block increases in output on exercise are ordinarily mediated through an increase in heart rate.[11] Failure of rate response requires an augmentation of stroke volume which, as in acquired heart block, may be inadequate.[12]

Temporary or permanent pacemaking has rarely been necessary in adult patients with congenital complete heart block,[13–17] and caution has been advised in deciding upon permanent pacing because of the transient nature of syncope[4] and its tendency to diminish in frequency with age.[6] Such was not the case with the patients reported herein, and pacing was advised because of arrhythmias likely to cause sudden death (ventricular fibrillation and ventricular asystole), refractory Adams-Stokes syncope and a low cardiac output state.

That the rate of dominant pacemaker discharge should be reduced with age is hardly unexpected. However, whether this inhibition results from ag-

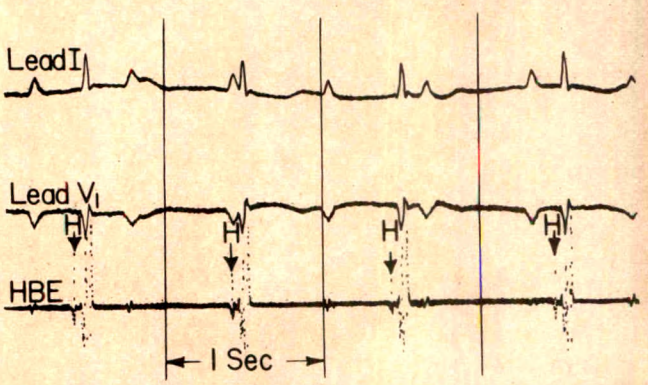

Figure 4. Case 7. His bundle electrogram (HBE) is recorded at 50 mm/sec paper speed. The His deflection (H) occurs at a normal interval of 62 msec from onset of the QRS complex.

TABLE II

Effect of Exercise and Administration of Atropine and Amyl Nitrite in 4 Patients with Congenital Complete Heart Block

Case no.	Resting Heart Rate (beats/min)	Exercise		Heart Rate (beats/min) with Atropine*	Heart Rate (beats/min) with Amyl Nitrite
		Heart Rate (beats/min)	O_2 Consumption (cc/min)		
1	60	107	2,650	62	107
2	65	115	3,200	72	102
6	47	105	2,400	55	118
7	68	120	3,250	81	110

* 1.2 mg given rapidly intravenously.

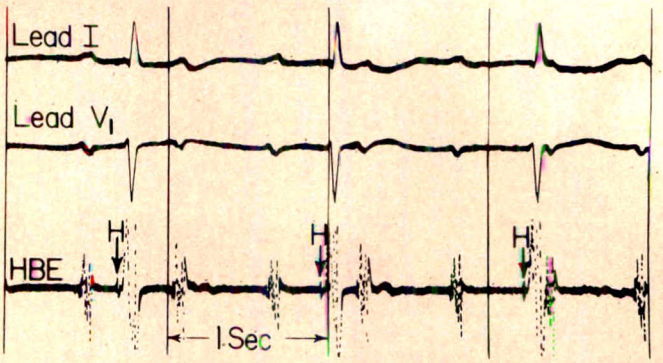

Figure 5. Case 9. His bundle recordings made at 50 mm/sec reveal a constant and shortened H–V interval of 32 msec.[20]

ing alone or from superimposed myocardial disease or impaired autonomic activity is not clear. To investigate the degree of autonomic impairment in congenital complete heart block, 5 subjects performed exercise on a treadmill, and 4 of these were studied after inhalation of amyl nitrite and intravenous administration of atropine (Table II). Although a considerable increase in ventricular rate was noted with exercise in all subjects, in none was the rate appropriate for the degree of oxygen consumed.[18] In 2 subjects (Cases 6 and 7) who underwent stress to maximal oxygen consumption, maximal heart rates were only 105 and 123/min. In all subjects studied a quantitatively similar rate acceleration occurred after inhalation of amyl nitrite.[19] However, no significant increase in rate occurred with administration of atropine, a finding previously noted by Narula et al.[2] and expected if the pacemaker origin is low in the bundle of His. These findings suggest that in some adult patients with congenital complete heart block there may be not only an anatomic disturbance of conduction but also depression of impulse formation in a low junctional pacemaker. This impaired autonomic activity appears to progress with age and is manifested both by a failure to respond to intravenously administered atropine and by a reduced sympathetic heart rate response to effort.

Finally, patients in this group have consistently fulfilled only 1 criterion of longevity, the absence of structural heart disease. Congenital complete heart block can be considered benign, therefore, only when a persistently rapid junctional pacemaker is identified. The tendency to deceleration of rate must be sought by clinical examination, stress testing and perhaps portable electrocardiographic monitoring. It is conceivable that identification of a higher and more stable junctional pacemaker through a more appropriate rate response to stimulation with intravenously administered atropine, exercise and inhalation of amyl nitrite may indicate a more stable clinical course in adult life.

Addendum

Since submission of this manuscript, another patient has been identified with apparent congenital complete heart block.

Case 9: A 49 year old contractor was hospitalized because of 2 episodes of sudden unconsciousness occurring over 18 months. A single episode of syncope had occurred 19 years previously. Rheumatic heart disease had been clinically suspected at age 3 years because of bradycardia and a heart murmur. On hospital admission the electrocardiogram was consistent with congenital complete heart block. History revealed dyspnea and effort fatigue of 2 years' duration. Cardiac catheterization revealed slightly increased left and right ventricular filling pressures and decreased cardiac output at rest and exercise. Coronary arteriography showed normal findings. Electrographic studies of the conduction system showed a low normal H–V interval of 32 msec[20] (Fig. 5). Maximal treadmill stress testing showed an increase of ventricular rate from 48 to 88/min with frequent ventricular premature beats at end of effort. Because of the poor response to ephedrine therapy, limited rate response of exercise, syncope and continued symptoms of low cardiac output, implantation of a permanent synchronous pacemaker has been recommended.

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Aneurysm of the Nonpatent Ductus Arteriosus

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Clinical and necropsy findings are described in a 6 week old infant with aneurysm of the ductus arteriosus. It was obliterated at the pulmonary arterial end and patent at the aortic end. Observations in this case and in 60 previously described cases of ductal aneurysm disclosed that 46 of the aneurysms occurred in infants less than 2 months old, 4 in children, and 11 in adults. The aortic end of the ductal aneurysm is always patent. The pulmonary arterial end may or may not be patent. Since complications (rupture, embolism or infection) tend to develop in nearly half of the ductal aneurysms, operative resection appears indicated.

Persistent patency of the ductus arteriosus is a common congenital cardiovascular malformation. Aneurysmal dilatation is an occasional complication of patent ductus arteriosus in adults. Aneurysm of the ductus arteriosus in infancy—in contrast to simple patency—is rare. However, such was the case in an infant we recently studied. Clinical and necropsy observations in this patient with ductal aneurysm and in those previously reported by others are described in this communication.

Report of Patient

A 52 day old white boy, the first-born of twins, delivered at a referring hospital, weighed 2.2 kg after a term gestation. At birth he showed flaccidity, cyanosis and regurgitation; Apgar scores were 2 and 8 at 1 and 5 minutes, respectively. Positive pressure respirator and intubation were required initially with spontaneous onset of respirations at 5 minutes. He had multiple congenital abnormalities including an elongated neck, cloudy cornea, low-set and posteriorly rotated ears, complete cleft palate, long thumbs, fetal hypospadius and undescended testes. No precordial murmur was ever heard. Chest roentgenogram (Fig. 1) showed cardiomegaly. A large convex shadow at the left base was initially thought to be thymus.

On day 1, the hematocrit was 33 vol percent; leukocyte and platelet counts and serum electrolytes, including calcium and phosphorus, were normal. Chromosome pattern was 46 XY without any structural abnormality.

Initially the infant was hypotonic, fed poorly and had respiratory difficulties. Barium swallow on day 12 ruled out tracheoesophageal fistula. The cardiac silhouette was smaller (Fig. 1). The shadow in the angle between the aortic knob and pulmonary trunk was still interpreted as representing thymus.

The baby continued to lose weight and by day 22 he began to vomit almost all feedings, necessitating parenteral fluids to maintain electrolyte and caloric balance. The next day a mass was palpated in the right upper quadrant of the abdomen, and upper gastrointestinal series demonstrated pyloric stenosis (Fig. 1). On the same day, he was trans-

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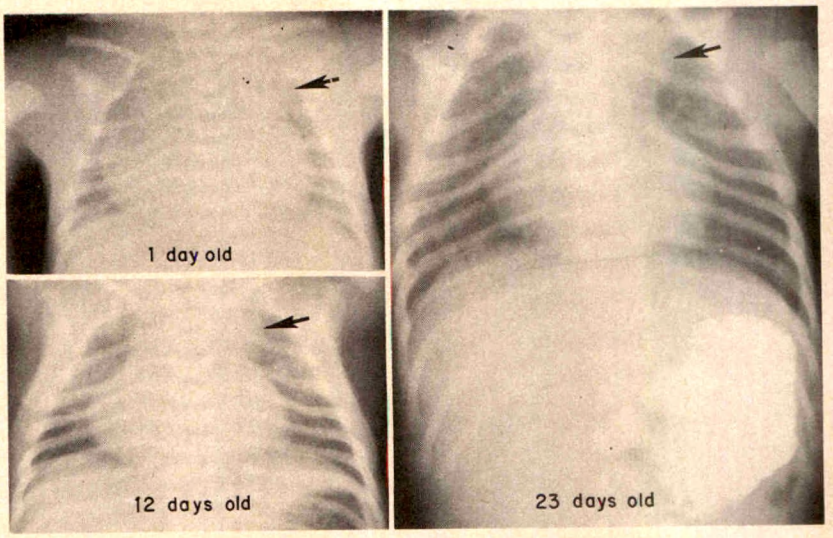

Figure 1. Chest roentgenograms. The arrows designate the ductal aneurysm. The cardiac size decreased from day 1 to day 23. Roentgenogram on the right demonstrates, in addition, pyloric stenosis with complete retention of contrast material 45 minutes after instillation of barium into the esophagus.

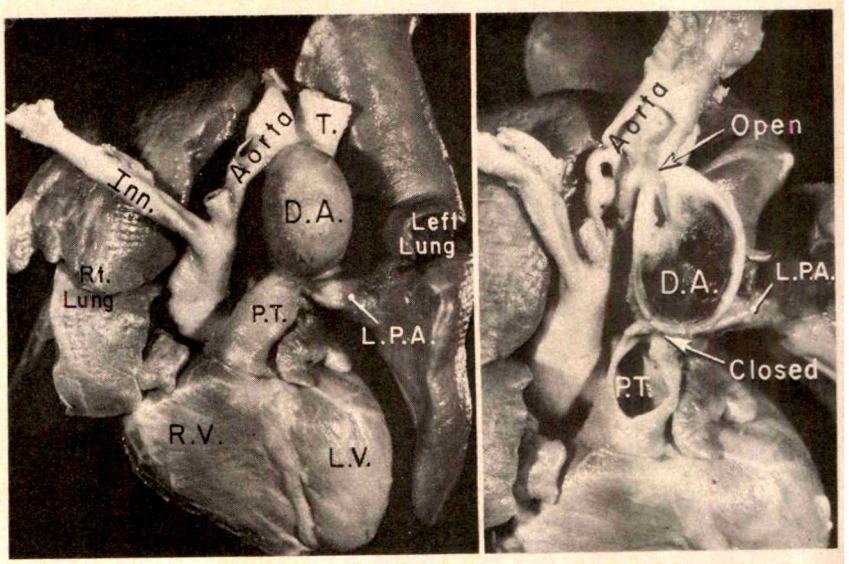

Figure 2. Unopened and opened views of the ductal aneurysm demonstrating its relation to surrounding structures. D.A. = ductal aneurysm; Inn. = innominate; L.P.A. = left main pulmonary artery; L.V. = left ventricle; P.T. = pulmonary trunk; R.V. = right ventricle; T. = trachea.

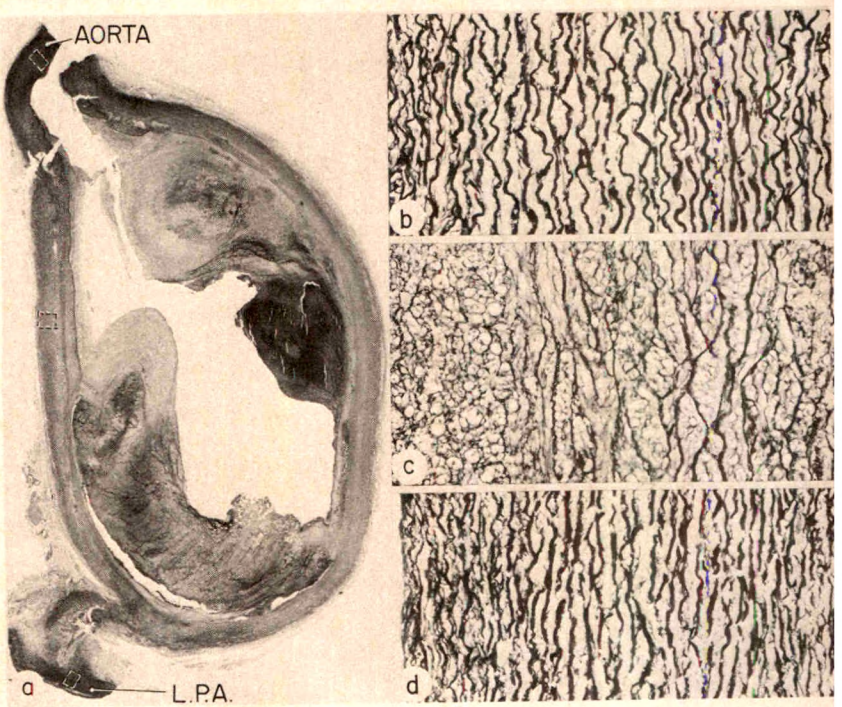

Figure 3. Photomicrographs of ductal aneurysm (**a**), and of portion of wall of aorta (**b**), ductal aneurysm (**c**) and left main pulmonary artery (L.P.A.) (**d**). The sites at which photomicrographs **b, c** and **d** were taken are shown by small blocks in **a.** The configuration of the elastic fibrils in the aorta (**b**) and left main pulmonary artery (**d**) are virtually identical. In contrast, fewer elastic fibrils are present in the wall of the ductal aneurysm (**c**), and the fibrils at this site have various spacial orientations. Movat stain, × 6 (**a**); elastic Van Gieson stains, each × 250 (**b** to **d**), all reduced by 43 percent.

TABLE I

Aneurysm of the Ductus Arteriosus

I. Patent aortic and pulmonary arterial ends
  A. Fusiform* (with or without aneurysmal thrombus)
    1. Infected[4,13,19,20,23,26]
    2. Noninfected[3,6–8,22,24,25,27,31,39,40]
  B. Tubular dilatation†[16,18,28]
  C. Dissection[10,12,21,27]
II. Nonpatent pulmonary arterial end
  A. Fusiform* (with or without aneurysmal thrombus)
    1. Infected[33,34]
    2. Noninfected[5,14,27,29,35–37,42,43]
III. Postoperative‡[52,53]

* Both aortic and pulmonary arterial openings are small in comparison to the diameter of the aneurysm.

† Openings into aorta and pulmonary artery are of similar diameter to that of the aneurysm.

‡ After operative ligation of a patent ductus arteriosus.

ferred to Georgetown University Hospital, and pyloromyotomy under local anesthesia was performed immediately. Postoperatively, he had several apneic spells and continued to feed poorly; poor Moro and suck reflexes and generalized hypotonicity persisted. He died without an obvious precipitating cause.

At necropsy, a 1.5 by 2 by 1 cm ductal aneurysm containing thrombus was found (Fig. 2). The pulmonary arterial end of the ductus was closed, and the aortic end was open. The wall of the aneurysm was composed primarily of smooth muscle and elastic fibrils; young connective tissue with focal calcific deposits was present at the junction of intraaneurysmal thrombus and ductal wall (Fig. 3). The right atrium was dilated, and the valve over the fossa ovale was incompetent. No evidence of rupture, embolism or infection of the aneurysm was present.

Discussion

Ductal aneurysm was described originally by Martin[1] in 1827 and by Billard[2] in 1828. Thore[3] in 1850 reported 8 cases of ductal aneurysm, and Hammerschlag[4] in 1925 reviewed the literature and excluded cases of aortic aneurysms involving the site of ductal insertion. Cruickshank and Marquis[5] in 1958 summarized the previous literature and added the tenth adult case.

At least 60 cases of ductal aneurysm have been reported.[1–43] The anatomic types are summarized in Table I and Figures 4 and 5. Exact anatomic classification is not possible in 19 cases[3,8,9,11,14,15,17,27,29,32] because of insufficient information regarding the status of the pulmonary arterial end of the ductus. Six cases[44–49] previously considered ductal aneurysm were excluded because of inadequate anatomic detail. Observations in the remaining 42 cases are summarized in Table II. Ductal aneurysm also may be classified by age—infantile, childhood and adult. Complications of the aneurysm in the 61 patients grouped by age are summarized in Table III and Figure 4.

Infantile ductal aneurysm: Nonpatent ductal aneurysm has been reported in 13 patients, includ-

TABLE II

Spontaneous* Aneurysm of the Ductus Arteriosus

Anatomic Classification	no.	Age Range	Complications: Rupture	Embolism	Infection	Assoc Mal
Patent ductal aneurysm						
Fusiform	19	2 days–51 yr	2	5	5	3†
Tubular dilatation	3	3 days–27 days	0	1	0	0
Dissection	7	12 hr–1 mo	3	0	0	1‡
Nonpatent ductal aneurysm						
Fusiform	13	13 days–66 yr	4	2	2	6§
Totals	42¶	12 hr–66 yr	9	8	7	10

* Excludes postoperative patients.

† Extrophie vesicale,[8] valvular incompetent patent foramen ovale,[31] aortic coarctation.[41]

‡ Hydrocele.[27]

§ Exomphalos,[27] double pelvis and ureter,[33] atresia of left pulmonary artery, stenosis of right pulmonary artery and aneurysm of pulmonary trunk,[36] right aortic arch,[39] coarctation of aorta.[42]

¶ Autopsy in 39.

Assoc Mal = associated congenital malformations

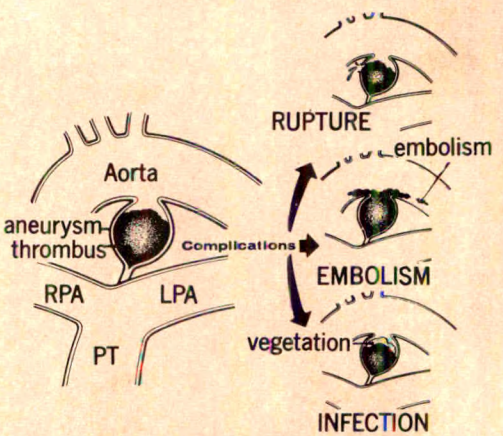

Figure 4. Diagram of aneurysm of the nonpatent ductus arteriosus and its complications. LPA = left main pulmonary artery; PT = pulmonary trunk; RPA = right main pulmonary artery.

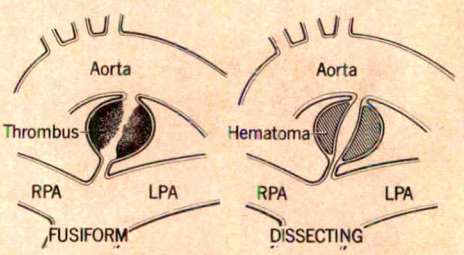

Figure 5. Diagram of aneurysm of the patent ductus arteriosus. In the fusiform aneurysm, the lumen contains thrombus which may or may not occlude blood flow. In the dissecting aneurysm a hematoma is present in the wall of the ductus but not in its lumen. Abbreviations as in Figure 4.

ing the infant described herein. The pulmonary arterial end was closed and the aortic end open in all 13. The pathogenesis of nonpatent ductal aneurysm is uncertain. Normally, the ductus arteriosus closes physiologically shortly after birth, but anatomic closure requires several days. By intimal proliferation[50] the ductus becomes obliterated first at the pulmonary arterial end, then the aortic end.[21,51] The walls of the ductus undergo involutional changes by a decrease in elastica in comparison with the pulmonary trunk and aorta, and by increase of fibrous connective tissue, giving rise to the ligamentum arteriosum. If closure of the aortic end is delayed, the ductus in effect becomes an aortic diverticulum, subject to systemic pressure at a time when its walls are undergoing involution. This circumstance favors dilatation of the patent portion of the ductus with subsequent aneurysm formation. This mechanism is the most attractive explanation of nonpatent ductal aneurysm in the infants described, all of whom were less than 2 months old. Necrosis of the walls of the ductus was thought to have been etiologically important in several cases[23,26,27] but was not present in our patient. In those cases in which the histologic features were presented, decrease in elastic tissue in the wall of the aneurysm was observed.

Adult ductal aneurysm: The origin of nonpatent ductal aneurysms in adults is less certain. Documented persistence into adulthood of an infantile ductal aneurysm is lacking. However, the anatomic similarities between adult and infantile ductal aneurysms suggest that the adult ductal aneurysm may represent persistence of the infantile variety. Other mechanisms have been proposed to explain adult nonpatent ductal aneurysm including trauma to a persistently patent ductus,[38–40] infective arteritis in a patient with subsequent inflammatory closure of the pulmonary arterial end,[33] and delayed spontaneous closure with arrest at the stage of obliteration of the pulmonary arterial end.

The latter mechanism, long considered the most likely one, was recently challenged by Bosman and Leoncini[42] as not being responsible by itself for aneurysm formation. These authors described a 66 year old man with a ductal aneurysm located just proximal to an aortic coarctation. They reasoned that in addition to obliteration of the pulmonary arterial end there must be some distal aortic obstruction causing increased systemic pressures in the patent portion of the ductus in order to initiate an aneurysm; 2 similar previously described patients were cited.[37,41] Perhaps this additional lesion is necessary in the genesis of aneurysm in some adults with arrest at the stage of obliteration of the pulmonary arterial end; the ductus under these circumstances has been subject to systemic pressure for a considerable period of time and there would not appear to be any stimulus for the walls to undergo involution. In fact,

TABLE III

Spontaneous* Aneurysm of the Ductus Arteriosus

Classification	no.	Age Range	Complications			
			Rupture	Embolism	Infection	Assoc Mal
Infantile[3,6–31]	46	12 hr–2 mo	5	6	5	5
Childhood[32–35]	4	20 mo–15 yr	3	1	1	1
Adult[4,5,36–43]	11	23 yr–66 yr	3	1	1	4
Totals	61†	12 hr–66 yr	11	8	7	10

* Excludes postoperative patients.
† Autopsy in 57.

in the majority of patients with isolated delayed spontaneous closure, the ductus appears as an inverted cone with the apex at the pulmonary arterial end and the base at the aortic end. Whether the pathogenesis of ductal aneurysm in childhood is the same as that operative in the infant or the adult remains uncertain.

Diagnosis: Correct antemortem diagnosis of ductal aneurysm has not been established in any infant. Because of the lack of related symptoms or physical signs, attention has not been drawn to the cardiovascular system in this age group. A soft tissue density at the upper border of the left cardiac silhouette may be mistaken for thymus, as it was in our patient (Fig. 1), or hilar adenopathy, as in Scheef's patient.[20] A nonpatent ductal aneurysm was established by angiocardiography and successfully resected in 1 patient[35] in the childhood group. The diagnosis has been made antemortem in only 1 adult patient.[43] The soft tissue density seen on chest roentgenogram was believed to represent aortic aneurysm in 2 patients,[5,42] and tumor of the mediastinum in a third.[38] Graham[38] incised a ductal aneurysm, having considered it to be a solid mediastinal tumor, and emphasized the importance of the correct diagnosis. He pointed out that the differential diagnosis of a mediastinal mass at the level of the pulmonary trunk with displacement of the trachea rightward must include ductal aneurysm.

Complications: Complications of ductal aneurysm resemble those of aortic aneurysm: rupture, embolism and infection. Of the 13 nonpatent ductal aneurysms reported (Table I), 4 ruptured, 2 embolized and 3 were infected. Death was directly attributable to 1 of these complications in 5 patients.[5,30,33,34,42] (The complication rate of the entire 61 patients was 43 percent, causing death in 19 patients [31 percent].)

Treatment: Tutassaura and Mustard[35] demonstrated the feasibility of total resection of a nonpatent ductal aneurysm, and there has been sufficient experience with postoperative ductal aneurysm[52,53] to encourage resection. Because of the high incidence of complications operative excision appears indicated.

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* Number of well documented cases of ductal aneurysm in this report. In the other cited references 1 case is described in each.

Respiratory Variation of Left Ventricular Ejection Time in Patients with Pericardial Effusion

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Left ventricular ejection times were measured by external carotid pulse tracing in 2 patients with pericardial effusion who had at most only an equivocal paradoxical pulse. Both patients demonstrated a 50 msec variation of ejection time with respiration at a constant heart rate. None of 10 control patients had variation in ejection time of more than 10 msec. These observations confirm the original observations of Weissler et al., who noted variations in left ventricular ejection time in a patient with pericardial effusion; the findings also indicate that such changes may be present when there is no significant paradox during intraarterial pressure recording.

Patients with pericardial disease may manifest an accentuation of the normal respiratory variation of the arterial blood pressure, that is, a paradoxical pulse. However, contrary to common belief, a paradoxical pulse is frequently absent or equivocal in patients who have constrictive pericarditis or a large long-standing pericardial effusion.[1] When present, this accentuated respiratory variation in the peripheral arterial blood pressure is thought to reflect changes in left ventricular stroke volume due to cyclic changes in left ventricular filling.[2] Our laboratory and others have shown that the left ventricular ejection time primarily reflects variations in stroke volume, although heart rate, left ventricular afterload and the inotropic state of the myocardium can also affect left ventricular ejection time independently of their effect on stroke volume.[3–5] Weissler et al.[6] reported variations in left ventricular ejection time in 3 patients with pericardial disease in 1961. It therefore seems reasonable to expect that the left ventricular ejection time may be of greater value than the peripheral arterial blood pressure in evaluating patients suspected of having pericardial disease. This report describes the findings in 2 patients who had large pericardial effusions but at most only equivocal paradoxical pulses.

Methods

Tracings of the external carotid pulse were recorded from 2 supine patients by an Electronics for Medicine, model A-161 pulse transducer coupled to an Electronics for Medicine polygraphic recorder. A simultaneous phonocardiogram was recorded from the second left intercostal space, enabling verification of the dicrotic notch. A pneumotachogram recorded the respiratory cycle of both patients before and after therapy. The excursions of the pneumotachogram were recorded during conscious but not forced respiration, causing a slight increase in excursion from that noted during unconscious respiration. Recordings were made at a paper speed of 75 to 100 mm/sec with superimposed time lines, each 0.04 or 0.02 second. Ejection time was measured from the onset of the

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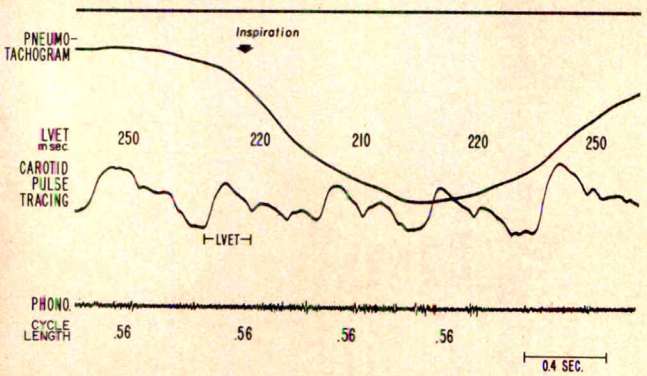

Figure 1. Case 1. The phonocardiogram demonstrates a 3-component pericardial rub. There is a 40 msec decrease in left ventricular ejection time (LVET) with inspiration at a constant heart rate.

steep portion of the carotid upstroke to the incisura of the dicrotic notch (Fig. 1).

Case Reports and Results

Case 1: A 28 year old white housewife described a 2 week history of fever and vague chest discomfort. The blood pressure was 120/80 mm Hg and, despite careful measurement, no paradox was discerned. Seven days after admission, a paradoxical pulse of 12 mm Hg with deep inspiration was recorded. A 2-component friction rub was easily audible; there were no gallop sounds. Chest roentgenogram demonstrated left pleural effusion and a marked increase in the cardiac silhouette suggestive of a pericardial effusion (Fig. 2A). Concomitant with administration of indomethacin for 2 weeks, the size of the cardiac silhouette decreased markedly and the patient became asymptomatic (Fig. 2B).

Figures 1 and 3 show pulse tracings recorded before and after therapy. Figure 4 demonstrates the initial 50 msec variation in ejection time at heart rates of 98 to 102 beats/min.

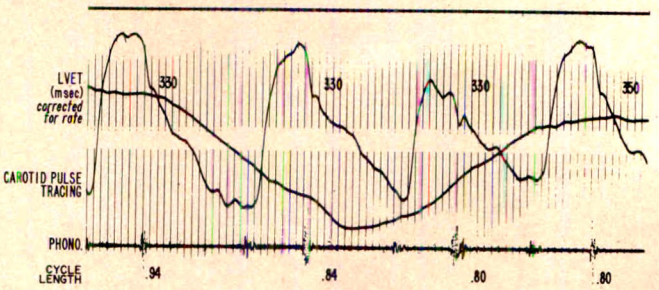

Figure 3. Case 1. Recordings 2 months after therapy. The phonocardiogram is now normal. There is a 20 msec variation in ejection time with inspiration.

Case 2: A 53 year old black woman presented with a history of progressive fatigue of 6 weeks' duration. At the time of hospital admission, a paradoxical pulse of 30 mm Hg was observed. The chest roentgenogram and heart isotope scan suggested massive pericardial effusion. Approximately 300 cc of serosanguineous fluid was removed with difficulty. During the next 7 days the patient had only 12 mm Hg of paradoxical pulse with deep respiration. Because of the bloody pericardial fluid and recently documented conversion of results of a purified protein derivative skin test from negative to positive, tuberculous pericarditis was suspected. Antitubercular therapy was instituted.

At surgery, approximately 700 cc of serosanguineous fluid was obtained from the pericardium, and both thickened parietal and visceral pericardii were removed. Microscopic examination demonstrated multiple tuberculous granulomata.

Recordings were made on several occasions before operation and 6 days after the pericardial stripping. Figure 5 exhibits a 50 msec respiratory variation in ejection time; the cardiac cycle varies only 20 msec. Figure 6A displays the intraarterial blood pressure tracing recorded simultaneously with a carotid pulse tracing after 3 days of diuretic therapy. Despite no significant respiratory changes in the intraarterial pressure, the ejection time varied 30 msec. The postopera-

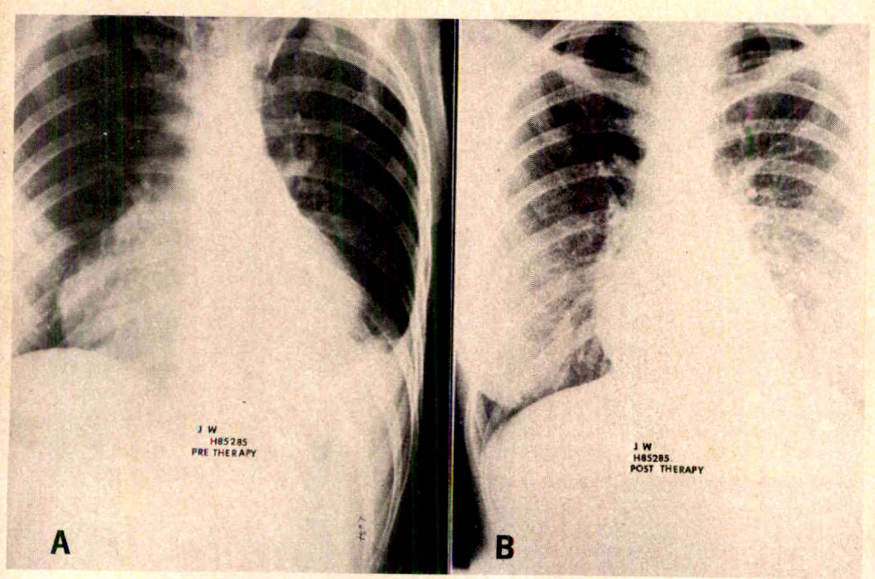

Figure 2. Case 2. **A,** admission teleoroentgenogram; **B,** teleoroentgenogram after 2 weeks of indomethacin therapy.

tive pulse tracing showed a variation in left ventricular ejection time of 10 msec (Fig. 6B).

Control Subjects

Carotid pulse tracings were recorded from 10 patients with various forms of heart disease during accentuated respiration. A cardiac diagnosis not involving the pericardium had been previously established in these patients by cardiac catheterization. No patient had a variation in ejection time of more than 10 msec. The roentgenogram (Fig. 7) and the pulse tracing (Fig. 8) of a patient with idiopathic myocardial hypertrophy and secondary mitral insufficiency with massive cardiomegaly and ascites are presented. Despite severe congestive heart failure, the ejection time varied only 10 msec.

Discussion

It has been demonstrated that the duration of left ventricular ejection time correlates closely with cardiac stroke output.[3–5] The paradoxical pulse in pericardial tamponade is produced by an exaggeration of the normal inspiratory decline in left ventricular stroke output[2]; however, the exact mechanism for this observation is still debated.[7,8] Whatever the pathophysiologic factors, one would expect the left ventricular ejection time to reflect this respiratory variation in left ventricular output.

Weissler et al.[6] reported that respiration caused a change in left ventricular ejection time of 10 msec or less in 120 patients, many of whom had congestive heart failure. We found a similar slight

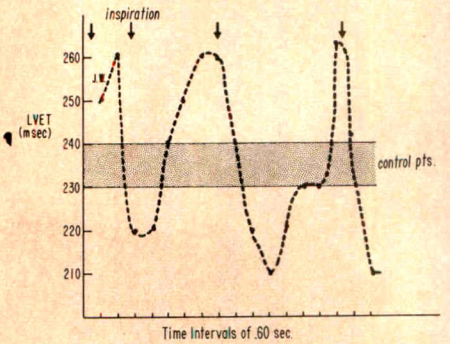

Figure 4. Case 1. The **dotted line** indicates the variation of left ventricular ejection time with respiration. The **shaded area** indicates the range of left ventricular ejection time in control patients but is not intended to reflect actual measurements in left ventricular ejection time.

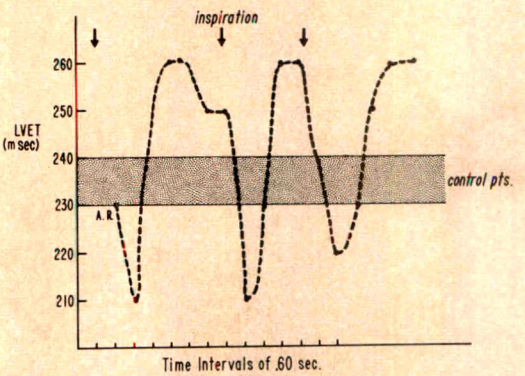

Figure 5. Case 2. See Figure 4 for explanation.

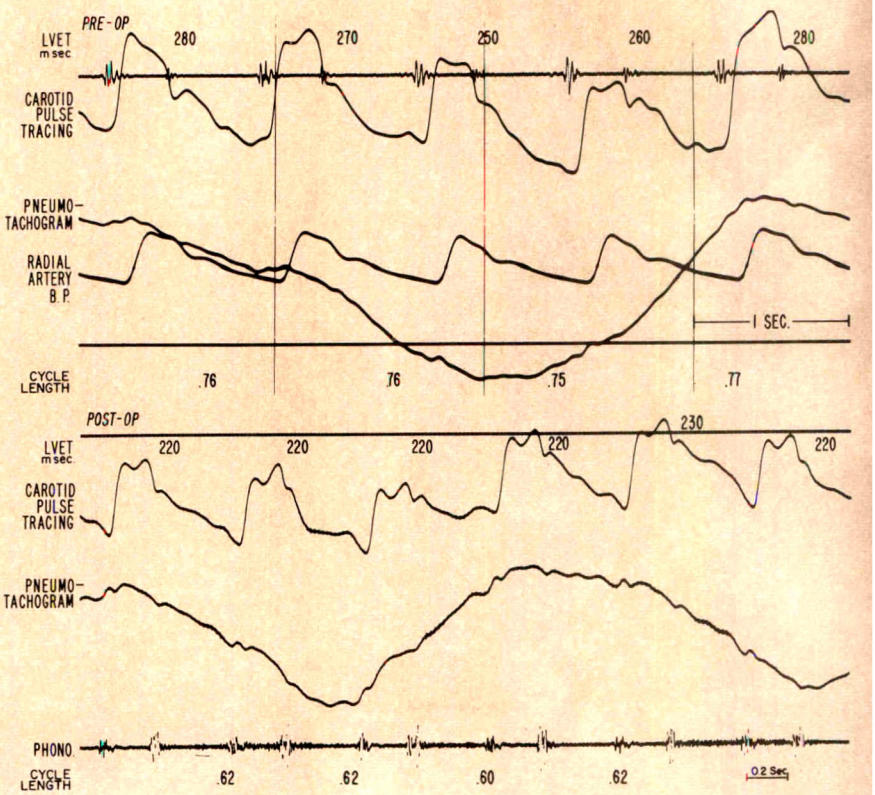

Figure 6. Case 2. **Top panel,** the preoperative pulse tracing demonstrates a 30 msec variation in left ventricular ejection time with respiration at a time when the intraarterial blood pressure varied minimally. **Bottom panel,** the postoperative tracing demonstrates a 10 msec variation of left ventricular ejection time with respiration. B.P. = blood pressure.

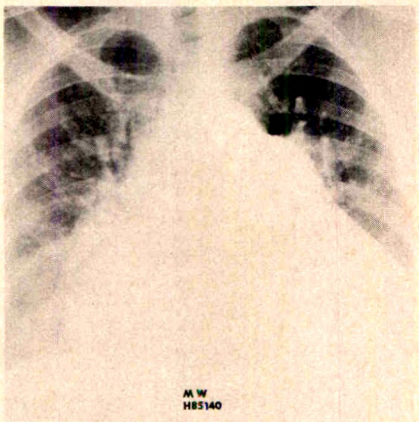

Figure 7. Teleoroentgenogram of a 50 year old patient with idiopathic myocardial hypertrophy, massive edema and hepatomegaly.

respiratory variation in left ventricular ejection time in a heterogeneous group of 10 patients, several of whom had severe congestive heart failure and massive cardiomegaly. Weissler and co-workers[6] found a variation in left ventricular ejection time from 25 to 50 msec in 2 patients who showed constrictive pericarditis and marked pulsus paradoxus, and in 1 patient with pericardial effusion and a respiratory variation in blood pressure of 8 mm Hg. Therefore, our study was undertaken to determine if a significant and characteristic respiratory variation of left ventricular ejection time occurred in patients with pericardial effusion.

In Case 2, we were able to detect respiratory changes of left ventricular ejection time of 30 msec at a time when only minor respiratory variation of blood pressure was detected by intraarterial recordings (Fig. 6). The obliteration of a significant respiratory variation of left ventricular ejection time after operation suggests that the abnormality is due to the pericardial effusion and not to factors such as obesity or lung disease, which can also induce a paradoxical pulse.

In Case 1 only a borderline paradoxical pulse was present. The disclosure of a 40 msec variation in left ventricular ejection time is evidence that

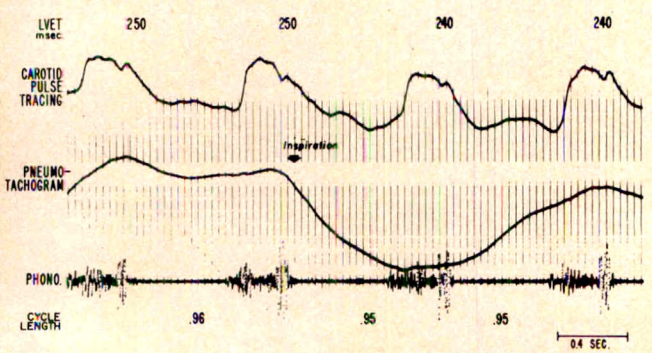

Figure 8. Same patient. Despite severe congestive heart failure, ejection time varies only 10 msec with deep inspiration.

this patient had a hemodynamically significant pericardial effusion. The rapid decrease in heart size to normal during indomethacin therapy is consistent with a clinical diagnosis of pericardial effusion. The left ventricular ejection time variation was 20 msec at a follow-up visit 2 months after therapy was discontinued. This variation is of questionable significance but could reflect slight persistent constriction. A respiratory variation is probably significant only if it is 30 msec or more. This figure should exceed any variation due to a normal 10 msec variation and the 10 msec range of error for human recording at a paper speed of 75 to 100 mm/sec.

The study by Weissler et al. of the ejection times in normal subjects and in patients with cardiac disease was performed during a level of quiet respiration which may have been different from that of our control group. Thus, left ventricular ejection time in the 10 patients with various types of heart disease was measured at conscious, slightly increased respiratory effort equivalent to that of our patients with paradoxical pulse. This method was used in an effort to establish and compare the variation of left ventricular ejection time in patients with other forms of heart disease with the variation observed in the patients with pericardial effusion. However, only with intrapleural pressure recording could one guarantee that the respiratory levels were identical.

The variation in heart rate during respiration was minimal and made it unnecessary to correct left ventricular ejection time for heart rate. In the presence of a significant sinus arrythmia, correction of left ventricular time for heart rate is mandatory. The Bazett formula (Left ventricular ejection time/R–R interval) may be an unreliable index of beat to beat variation in stroke volume if marked variation of the R–R interval is present. In such a case, correction of the left ventricular ejection time should be made by the more complex formula of Weissler et al.,[3] which expresses the observed changes as deviations from expected normal values.

Patients who have severe congestive heart failure and pulsus alterans are expected to show some variation in ejection time from beat to beat, but this variation is not parallel with respiration. The presence of marked obesity or obstructive lung disease can be associated with a respiratory variation in systolic pressure, but we have not observed respiratory variation of ejection time with heart failure alone. This is consistent with results of previous studies which demonstrated that, in patients with obstructive lung disease, respiratory variations in systolic pressure will occur without simultaneous changes in pulse pressure or stroke volume.[2,8]

Clinical applications: Measurement of the ejection times during respiration appears to be useful

in evaluating patients with suspected pericardial effusion. Obviously, large numbers of different subgroups of patients with congestive heart failure must be studied to establish the range of respiratory variation in left ventricular ejection time before one can say that the findings described clearly separate heart failure from pericarditis with effusion. Patients with severe failure may have small pericardial effusions. Since these are hemodynamically insignificant, it seems unlikely that they would affect the left ventricular ejection time. However, our study suggests that the measurement of left ventricular ejection time not only is a useful method in establishing the diagnosis of pericardial disease, but also is an objective measurement by which one can evaluate therapy.

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Beta Adrenergic Blockade, 1972

Pharmacology and Clinical Uses

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For several decades, investigators have considered the possibility that sympathetic nervous system activity and the effects of catecholamine administration were mediated through receptor mechanisms. Ahlquist,[1] in 1948, first presented scientific evidence to document the concept of receptor mechanisms for the action of catecholamines. His hypothesis was based on the graded sensitivity in neuromuscular responses of a variety of tissues to different vasoactive amines. He described a system of 2 major types of receptors, alpha and beta, operative in many mammalian systems. The introduction of phenoxybenzamine in the 1950's as a specific blocker of the alpha receptor supported some of the postulates of Ahlquist, and Powell and Slater[2] in 1958 reported the use of dichloroisoproterenol as a specific beta blocker, clearly confirming the basic tenets of the theory. However, dichloroisoproterenol was never used in clinical medicine because of its initial properties of stimulating the beta receptor before blocking it. Since 1960, a number of other specific beta-adrenergic blocking agents have been developed.[3,4]

The introduction of, and the basic and clinical studies with, these new classes of beta adrenergic blocking drugs has led to a better understanding of cardiovascular physiology in health and disease. For example, the study of arrhythmias has been advanced through the use of beta adrenergic blocking drugs as a means of defining the action of catecholamines on conduction velocities, atrioventricular conduction, arrhythmia threshold and intracellular action potentials. In angina pectoris, laboratory and clinical studies with beta blocking drugs have provided important tools which have led to better understanding of the role of heart rate, contractile state, afterload, and preload in myocardial oxygen consumption. In idiopathic subaortic stenosis, the responsiveness of the left ventricular outflow tract obstruction to catecholamines, and the blocking of this action by specific beta adrenergic blocking drugs, has produced a physiologic understanding of this important clinical entity. Beta blocking drugs have also been utilized in studies that clarify the interrelation of thyrotoxicosis and the autonomic nervous system activity, in understanding factors which control peripheral vascular resistance, and in developing better understanding of agents which influence the inotropic state of the myocardium.[3]

Clearly, these agents are extremely important for managing patients with heart disease, and their use has provided us with widened horizons for understanding the role of the sympathetic nervous system in disease.

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Basic Pharmacology

The concept of beta adrenergic blockade remains a pharmacologic one, with the definition relating to the potency of any particular agent to block the specific and selective beta adrenergic stimulating properties of the prototypical catecholamine, isoproterenol. Although biochemical and electron microscopic studies have not clearly revealed the character of the receptor mechanisms, recent studies have shown that a microsomal fraction of canine ventricular myocardium concentrates radioactive-labeled norepinephrine.[5] This bound norepinephrine could be displaced by beta adrenergic stimulating catecholamines and by propranolol, a specific beta adrenergic blocking drug. Thus, it was postulated that these microsomal particles contain the beta adrenergic receptor.

At present, more than 16 drugs with beta adrenergic blocking properties have been developed and studied in laboratories throughout the world.[3] Many of these compounds have both specific beta adrenergic receptor blocking actions and direct action, or "membrane-like" activities. An understanding of both of these properties is important in defining the action of these drugs in the treatment of disease. For propranolol and alprenolol, 2 specific isomers, *d*- and *l*-, have been described. The *d*-isomers have few beta blocking properties, but have membrane effects. The *l*-isomers have almost no membrane effects, and have potent beta block-

ing properties. Drugs such as Sotalol and practolol have no membrane effects, and the recently introduced drug, practolol, is relatively cardiospecific. These agents block the stimulating actions of catecholamines on the heart; that is, they block the increased heart rate, rate of pressure development in the ventricle, contractile state and cardiac output, as well as the peripheral vasodilatation produced by norepinephrine and isoproterenol. Other neuromuscular sites in mammalian tissue also have beta receptors, and their stimulation is blocked by these agents.[3]

Several thousand papers are published yearly describing studies with the use of beta blocking drugs. Clinical studies utilizing these drugs have been carried out throughout the world. In most countries in Europe, Asia and Africa, a variety of beta blocking drugs are available for the treatment of patients with cardiovascular disorders. However, in the United States, propranolol is the only beta adrenergic blocking agent that has been approved by the Federal Food and Drug Administration for the treatment of disease in man. Its use has been restricted to the treatment of arrhythmias, complications of pheochromocytoma and hypertrophic subaortic stenosis. Nevertheless, a number of investigational studies in this country have demonstrated the beneficial effects of propranolol and other beta adrenergic blocking drugs in angina pectoris and have provided a new physiologic approach to its treatment and prevention in many patients.

Clinical Applications

Propranolol, which has both beta blocking and "membrane-like" properties, has been the most extensively studied agent for the treatment of disease in man. Practolol, Sotalol®, oxprenolol, alprenolol and other compounds have also been studied. The following summary of the general clinical applications of beta blocking drugs relates primarily to propranolol.

Arrhythmias[6]: Both the membrane and beta blocking properties of propranolol are operative in the treatment of cardiac arrhythmias. Its use for the treatment and prevention of almost every known cardiac arrhythmia has been reported. However, for the treatment of arrhythmias, propranolol is an agent of secondary importance. The specific situations that indicate its use include arrhythmias induced by the administration of catecholamines; atrial fibrillation and atrial flutter; conditions in which digitalis cannot be administered in doses large enough to produce high degrees of atrioventricular block and adequate slowing of the ventricular rate; interruption of refractory paroxysmal tachycardias; treatment of digitalis intoxication producing atrial tachycardias and ventricular arrhythmias; and in paroxysmal arrhythmias that occur after cardiac surgery, due either to digitalis intoxication or to electrolyte abnormalities. In patients with the latter arrhythmias, the drug should be administered with caution, since the sympathetic drive to the heart is essential for survival. We have recommended intravenous doses of 1 mg, given every 5 minutes for a total of 3 doses, or a total of 3 mg. An alternative method is the administration in most patients of 100 to 200 μg/kg over a period of 10 minutes.

Beta blocking drugs have also been used with reported beneficial effects for the prevention of arrhythmias. These include refractory paroxysmal atrial tachycardias, atrial fibrillation and atrial flutter; when these paroxysmal arrhythmias are associated with the Wolff-Parkinson-White syndrome, propranolol has been demonstrated to be uniquely beneficial. In patients with metastatic pheochromocytoma, and in patients with recurrent ventricular tachycardia, beta blockade may be useful. For the prevention of arrhythmias, propranolol is usually started with 40 mg/day in divided doses and increased up to a dose of 240 mg/day.

Angina pectoris[3]: Beta adrenergic blockade provides a unique physiologic approach for treating patients with angina pectoris. In the treatment of these patients, beta blocking drugs have potentially helpful and potentially harmful effects. The vector of these opposing forces determines whether or not the drug will be beneficial. Its potentially helpful effects include a reduction in heart rate and in the heart rate response to exercise, a decrease in the rate at which ventricular pressure is developed, a slight reduction in cardiac output, and a reduction in the elevation of blood pressure which occurs with exercise. All of these effects reduce myocardial oxygen demands and therefore would be expected to benefit the patient with angina pectoris. On the other hand, beta blockade frequently results in an increase in left ventricular diastolic pressure and ventricular volume and in the precipitation of congestive heart failure in patients with severe myocardial damage. These effects would be potentially harmful. Generally, propranolol has greater beneficial effects in those patients in whom extensive myocardial damage has not been produced by the atherosclerotic coronary disease.

The unique physiologic advantage of beta blockade in angina pectoris is due to the reduction in myocardial oxygen demands, especially during exercise. This allows a patient to do more external work, while requiring decreased myocardial oxygen delivery, thus delaying the onset of ischemia and the occurrence of angina pectoris. When it is used in conjunction with isosorbide dinitrite, we have observed that 70 to 80 percent of patients selected for propranolol therapy benefit from it. Similar results have been reported for alprenolol, practolol, Sotalol and oxprenolol. In most countries other than the United States, all of these agents are available for the treatment of angina pectoris.

Myocardial infarction: While great care must be exercised in the use of beta blocking drugs in acute myocardial infarction, small doses of propranolol (1 to 3 mg total intravenously) have been reported to be successful in preventing arrhythmias associated with myocardial infarction. The initial enthusiasm for the prophylactic administration of the drug in acute myocardial infarction, which resulted from reports from England showing drastic reductions in mortality, has been questioned, and studies showing no beneficial effects predominate at this time. Recent studies in animal preparations have suggested that propranolol may alter the size of an infarct by decreasing the damage to viable myocardial cells adjacent to the infarct. This benefit apparently results from the inhibition by beta blocking drugs of the sympathetic discharge of circulating catecholamines which deleteriously affect partially viable myocardial tissue. Further studies are needed to characterize this action of beta blockade in myocardial infarction. At the present time, it seems wise to conclude that, in general, beta blocking drugs should not be used in acute myocardial infarction, except under controlled conditions in a coronary care unit, and by those with great experience in their utilization.

Idiopathic hypertrophic subaortic stenosis: The left ventricular outflow obstruction in patients with this disorder is dynamic. We have recently characterized patients as having latent obstruction, labile obstruction and fixed obstruction, with a vicious cycle leading to progression of the disease.[7] Catecholamine stimulation results in increased outflow tract obstruction in most patients with this cardiomyopathy. It is postulated that in labile and latent states, intrinsic increases in sympathetic activity produced by exercise or emotion may also increase the level of obstruction, thereby producing increased hypertrophy. Interruption of this sympathetically mediated increased obstruction can be prevented by the administration of effective beta adrenergic blocking agents. This has been demonstrated in a number of hemodynamic studies. Thus, it is our present practice to administer propranolol on a long-term basis to patients with latent and labile obstruction when it has been demonstrated at cardiac catheterization that the obstruction is increased by catecholamine administration. As yet, no definite long-term studies have documented this mode of therapy to be beneficial. In most of our patients, there is a decrease in symptoms and in the severity of cardiac disease.

Hypertension: The interrelation of the autonomic nervous system and hypertension has received increasing emphasis during the past several years. Several studies have demonstrated that blood pressure may be successfully lowered by the administration of beta blocking drugs. This effect is most frequently related to a decrease in cardiac output without significant change in peripheral vascular resistance. Controversy regarding the exact mechanism by which these agents decrease blood pressure still exists, and further studies are needed to characterize the action of beta blocking agents in hypertension before their widespread utilization for this purpose.

Other conditions: Many other clinical conditions, including pheochromocytoma, thyrotoxicosis, outflow tract obstruction of the right ventricle, tetralogy of Fallot, hyperkinetic states, anxiety, Parkinsonism, and the like have been treated with beta adrenergic blocking drugs. We have summarized the rationale and results of these studies in a previous publication.[3]

Side Effects and Contraindications

A number of side effects have been reported in patients undergoing treatment with beta blocking agents. These include skin rashes, nausea and vomiting, diarrhea, purpura and a decreased metabolic response to hypoglycemic attacks in diabetes mellitus. Major side effects, such as extreme bradycardia, the precipitation of congestive heart failure, heart block and cardiogenic shock, have been reported in patients with severe cardiac disease. A physiologic understanding of the action of beta blocking agents on the sympathetic nervous system allows one to anticipate situations of probable serious side effects. In patients with cardiogenic shock and latent or overt congestive heart failure, these agents should not be used, since the sympathetic nervous system is exerting maximal effect on the ventricular myocardium. In heart block, chronic obstructive lung disease and acute asthma, beta blockade is contraindicated. Occasional difficulties with slow idioventricular rhythm have been encountered after cardioversion in patients receiving large doses of beta blocking drugs. The agent should be discontinued 72 hours before operation in patients undergoing elective cardiovascular surgery, since difficulties in starting and maintaining the heart at the termination of such procedures have been reported in patients receiving large doses of beta adrenergic blocking drugs.

Future Developments

The introduction of these agents and studies with them have led to important physiologic and biochemical advances in our knowledge of the role of the sympathetic nervous system in health and in disease. It seems likely that more basic understanding may result from their continued study. A better appreciation of receptor mechanisms and their biochemical identification seems likely. It also seems possible that greater appreciation of the role of the sympathetic nervous system as compensation for conditions of decreased myocardial performance will result from laboratory and clinical studies with beta blocking drugs. Furthermore,

separation of the inotropic and chronotropic actions of these drugs by chemical techniques of synthesizing different types of molecules may well result in development of drugs that act specifically for one or the other purpose. Recent studies have suggested that this separation may be possible. In a search for pharmacologic agents with specific membrane properties, some of the isomers of new beta blocking drugs may allow a better separation of membrane effects from beta blocking effects. The need for a new long-term or antiarrhythmic agent is apparent to many investigators in cardiology, and it seems possible that an entirely new class of drugs may be developed along the lines of the *d*-isomers of some of the more important beta blocking drugs.

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Action and Nomenclature of Nitroglycerin and Nitrate Esters

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Sublingually administered nitroglycerin has remained for nearly a century the most effective and dependable drug for the treatment of coronary artery insufficiency. Recently, extensive investigations into the mechanism of action of nitroglycerin have substantiated that this agent is a potent coronary vasodilator; in addition, new suggestions indicate that a peripheral hemodynamic effect may also play an important role in its overall therapeutic value. Aside from the use of nitroglycerin to relieve the acute anginal attack, it is now recognized that the drug may be employed prophylactically when a stress-inducing activity is anticipated.

Today sublingually administered nitroglycerin maintains its preeminent position in the management of coronary insufficiency. However, the agent does not provide sustained action and repeated dosing with as many as 30 sublingual tablets in a day may be required. This prompted the pharmaceutical industry to develop long-acting coronary dilators that provide the beneficial actions of nitroglycerin and eliminate the disadvantage of repetitious dosing.

Research has proceeded along 2 distinct paths. The first approach was to look for a new compound pharmacologically like nitroglycerin although exhibiting a longer duration of action resulting from inherent chemical activity. Such efforts have resulted in the development of agents like isosorbide dinitrate (Isordil® and Sorbitrate®) and pentaerythritol tetranitrate (Peritrate®), the so-called long-acting organic nitrates. These agents, available orally, have a somewhat delayed onset of action when compared with nitroglycerin but they show demonstrable effects well after sublingually administered nitroglycerin is rendered inactive. An entirely different approach was to utilize nitroglycerin itself, thus retaining its proved therapeutic activity and prolonging its pharmacologic half-life by pharmaceutical processes.

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Recent advances in pharmaceutical technology have resulted in the preparation of time-disintegration granules of nitroglycerin such as Nitrong®, which provide a controlled-release therapeutic dose over a prolonged period. This achievement has been documented by human blood level studies as well as other objective physiologic measurements employed in angiologic research. These experimental data clearly negate older erroneous concepts concerning poor absorption of orally administered nitroglycerin.

It is clear that sublingually administered nitroglycerin bypasses the portal circulation and thus prevents degradation by the liver. Despite the degradation of orally administered nitroglycerin, adequate therapeutic amounts of the drug may be available. This appears to be the case from studies by Krantz et al.[1] which indicate that only a fraction of the administered dose is required for optimal dilatation of the coronary vessels. These workers perfused the coronary vessels of the isolated rabbit heart (Langendorff preparation) with a known concentration of nitroglycerin and found that only 14 percent of the administered dose was retained by the heart; the remainder was recovered unchanged in the perfusate. This finding may also apply to the intact system, suggesting that only minute quantities of unaltered nitroglycerin are necessary to evoke a maximal response in man after oral administration. These sustained-action forms of nitroglycerin have been classified as long-acting organic nitrates. Although the sustained-action device delays the rate of absorption of nitroglycerin, it does not alter its structure. Therefore, it is desirable to differentiate the true long-acting organic nitrates, such as isosorbide dinitrate and pentaerythritol tetranitrate, from those products that provide a controlled release of nitroglycerin.

Classification of antianginal drugs: Although many existing classifications attempt to distinguish between the various antianginal drugs, they are often not based on objective experimental findings and thus only add confusion to a controversial subject. I wish to propose a new classification based upon structure, pharmacology and therapy. This may be accomplished by establishing a set of criteria by which candidate drugs may be assigned to the most meaningful class. These criteria should include (1) chemical composition, (2) mechanism of antianginal action, (3) onset and duration of action, and (4) clinical application (Table I).

Pharmacology of antianginal drugs: This is perhaps the most elusive field in terms of reliable,

TABLE I

Antianginal Therapy

I. For the acute anginal attack
(criterion: rapid onset)
A. Sublingual administration
1. Nitroglycerin
2. Isosorbide dinitrate
B. Inhalation
1. Amyl nitrite
II. For the prophylaxis of angina pectoris
(criterion: prolonged action)
A. Oral administration
1. Inherently long-acting (pharmacologic mechanism): isosorbide dinitrate (Isordil®, Sorbitrate®), pentaerythritol tetranitrate (Peritrate®)
2. Inherently short-acting, made sustained-release (pharmaceutical mechanism): controlled-release nitroglycerin (Nitrong®)
3. Inherently long-acting, made sustained-release (pharmaceutical mechanism): isosorbide dinitrate, pentaerythritol tetranitrate

straightforward experimental methods. The nature of the clinical disorder itself is such that quantification of its course is difficult to document. The significant emotional component, which introduces variables such as patient-physician rapport, environmental factors and placebo effect, must be carefully considered.

The pharmacologist searches for the objective measure of drug action and attempts to limit variables while ensuring their statistical predictability. Such an approach can be found in applications of plethysmographic methodology to cardiovascular research. Modifications of this procedure have been successfully adapted to man by Winsor,[2] who measures finger pulse contour alterations and by Mason and co-workers,[3,4] whose venous occlusion technique has provided strong support for an extracoronary mechanism of nitrate action. Dilatation of peripheral vessels, both arterial and venous, leads to pooling of blood in the capacitance reservoir, thus decreasing the functional circulating volume. Five minutes after oral administration of 5 mg of isosorbide dinitrate plethysmographic action began and continued for 1 hour. The orally administered controlled-release nitroglycerin tablet provided a duration of physiologic action for at least 7 hours (the period for which measurements were taken during the study) as reflected by pulse contour measurements.[2] A similar end result has been reported by Parker et al.[5] with their method of femoral phlebotomy.

Quantitative coronary angiography: Sones and Shirey[6] used coronary cinearteriography to measure the degree of coronary vasodilatation after administration of nitroglycerin. Gensini and Kelly[7] further improved this technique by adding quantitative measurement of the lumen diameter and then feeding this information into a computer. This approach to the pharmacology of antianginal agents has demonstrated that sublingually administered nitroglycerin,[6] orally administered isosorbide dinitrate[8] and controlled-release nitroglycerin[9] actively dilate the coronary vessels.

Gensini[9] reported a mean increase in lumen diameter of the capacitance vessels of the coronary arteries of 8.4 percent for the group swallowing tablets of 10 mg of isosorbide dinitrate. For those receiving sublingual doses of 5 mg of isosorbide dinitrate or the 5 mg tablet to be chewed and swallowed, the mean vasodilation was 15.2 and 16.6 percent, respectively. The time of analysis was 5 to 12 minutes after drug administration. For the group receiving the oral tablet of 2.6 mg of controlled -release nitroglycerin, the mean vasodilatation 1 hour after administration was 14.1 percent.

Such action may lead to increased collateral circulation, thus aiding in the reinstitution of balanced flow to the ischemic myocardium. Although recent workers have detracted from the role of direct coronary vasodilation as a result of incongruities between antianginal efficacy and effects on coronary blood flow, quantitative angiography may help to reemphasize the importance of coronary vasodilation.

Electrocardiographic stress tests: A third area of investigation has lately received attention in the study of the clinical value of drugs in management of angina pectoris. This approach makes use of the standard electrocardiogram and several sophisticated variations. Specific ischemic patterns have been identified in patients with angina at rest and during stress, and it is the action of a drug in reversing this electrocardiographic indication of coronary artery disease that is evaluated. Master and Rosenfeld[10] studied the effects of a controlled stress by the 2-step method for the induction of S–T segment depression in the susceptible subject. More recently, portable continuous electrocardiographic monitoring units have been developed which enable the physician to study his patient around the clock. This telemetric technique specifically lends itself to drug testing by virtue of the "normal" conditions under which this procedure can be performed. Perhaps most important is the objective indication as shown by the electrocardiogram of myocardial ischemia rather than the patient's subjective and often unreliable record keeping.

Dynamic electrocardiographic studies undertaken by Karpman[11] and Bleifer[12] have indicated that isosorbide dinitrate significantly improves the S–T segment in angina patients. In similar studies with orally administered controlled-release nitroglycerin Winsor[13] demonstrated a significant protective effect against ischemic S–T depression in patients monitored throughout the day.

The double-blind clinical study: This technique is presently purported to represent the most informative of investigative methods. It depends primarily upon the patient reporting his own condition and is thus open to many unpredictable variables. According to the criteria used, certain dis-

tinguishing characteristics as well as specific functional similarities immediately become apparent regarding the long-acting nitrates and controlled-release nitroglycerin.

Nature of prolonged pharmacologic and clinical action: Most critical is the nature of the prolonged action of these agents. Both isosorbide dinitrate and pentaerythritol tetranitrate are considered long-acting by virtue of their unique inherent chemical and pharmacologic activity. The duration of cardiovascular activity is thus inseparable from the basic pharmacodynamic profile. Controlled-release nitroglycerin, on the other hand, demonstrates the same pharmacologic and metabolic characteristics as sublingually administered nitroglycerin, differing in its prolonged effect which has been provided by a pharmaceutical method.

Perhaps more important than the mechanism of prolonged pharmacologic activity is the nature of this activity in the light of the therapeutic value of these agents in the treatment of coronary insufficiency. When considering how these drugs act and why they relieve the pain of angina pectoris, one is impressed by the functional similarities among compounds rather than by any distinguishing qualities.

An impressive literature has been accumulated on the mechanism of antianginal action of various agents. Two theories are presently receiving a great deal of attention. The first and traditional view is that antianginal compounds increase the luminal diameter of the capacitance vessels of the coronary tree, thus decreasing the oxygen deficit in the ischemic areas of the myocardium. Coronary cinearteriographic studies[14] show direct coronary vasodilatation after administration of sublingually administered nitroglycerin and orally administered controlled-release nitroglycerin and isosorbide dinitrate. These 3 agents demonstrate a significant activity upon the coronary arteries, and this effect may explain their value in angina.

The gastrointestinal absorption of oral controlled-release nitroglycerin has been adequately demonstrated.[14–16] With regard to quantitative findings, Winsor[15] and Hirshleifer[16] have performed blood flow studies employing the finger and forearm plethysmograph, respectively. These results show that sublingually administered nitroglycerin and orally administered controlled-release nitroglycerin and isosorbide dinitrate demonstrate substantial plethysmographic activity, differing only in onset and duration of action.

Controlled-release nitroglycerin exhibits the same pharmacodynamic action as sublingually administered nitroglycerin, extending the period of drug effect[13] over many hours. Although the chemical structure of isosorbide dinitrate is distinctly different from that of nitroglycerin, it has retained similar pharmacologic characteristics as nitroglycerin, which are assumed to result from the mutual presence of the nitrate ester moiety.

In summary, a new classification for the antianginal drugs is suggested, establishing a set of criteria for a meaningful class designation. This classification more clearly emphasizes the similarities and differences among the various agents under consideration. More objective methods in angiologic research relying more upon physiologic indexes and less upon subjective patient reports are also advocated.

One who has watched this field of medicine change from empiricism to scientific exactness is still awed by the fact that nitroglycerin, the active ingredient in dynamite, dilates the coronary vessels. At present, this remains an enigma enveloped in an inscrutable puzzle. Perhaps some day the puzzle will yield to the researches of man.

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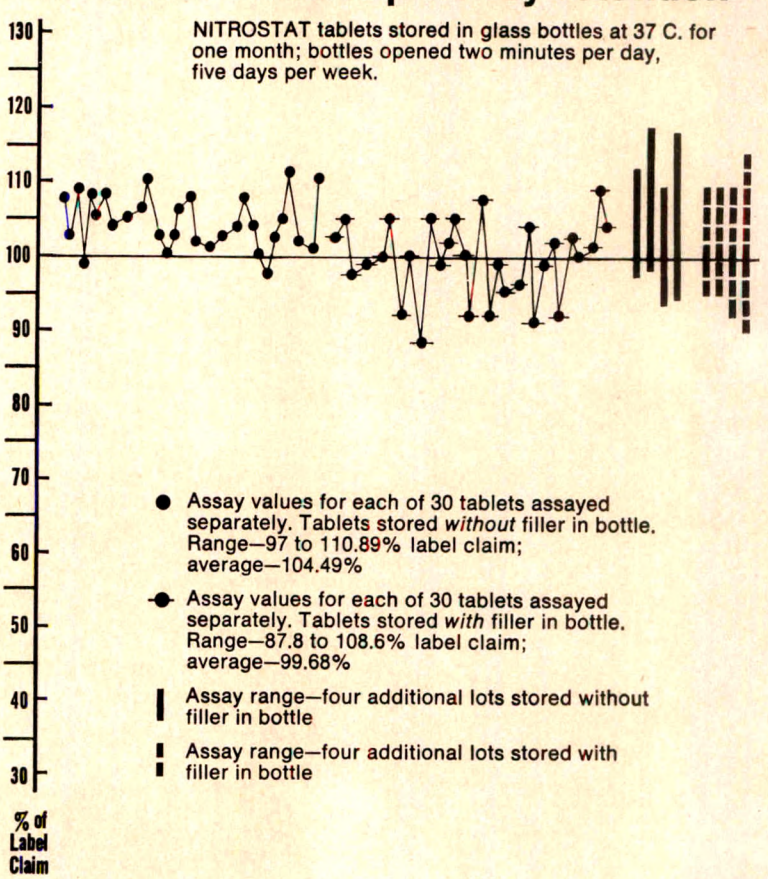

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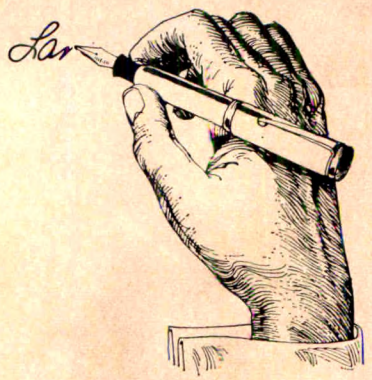
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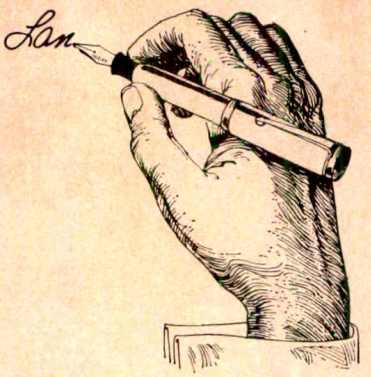
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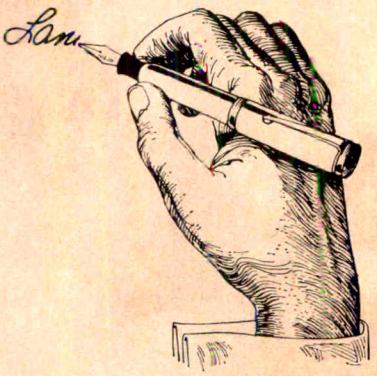
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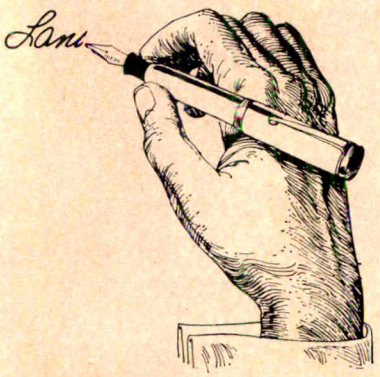
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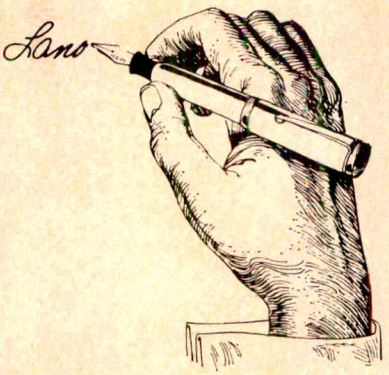
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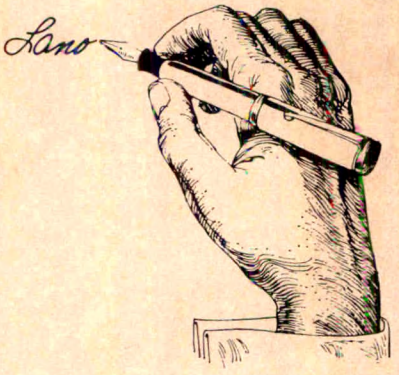
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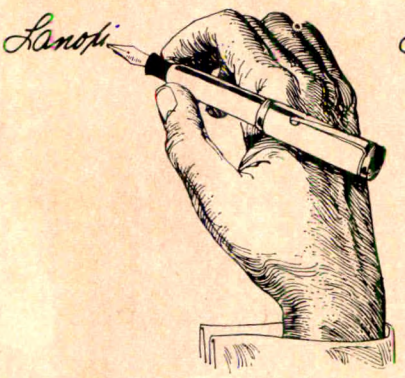
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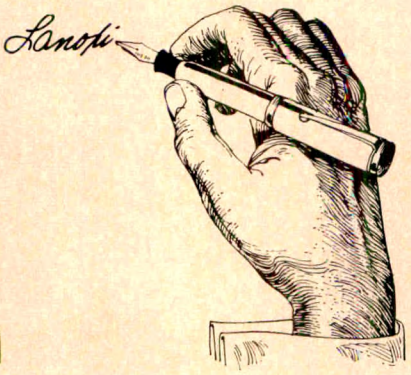
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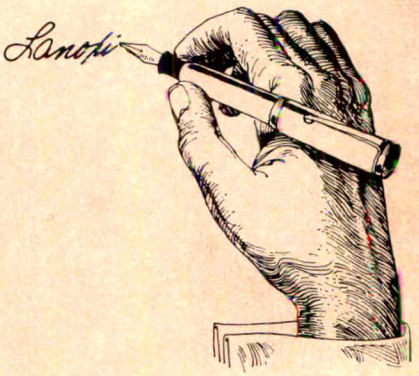
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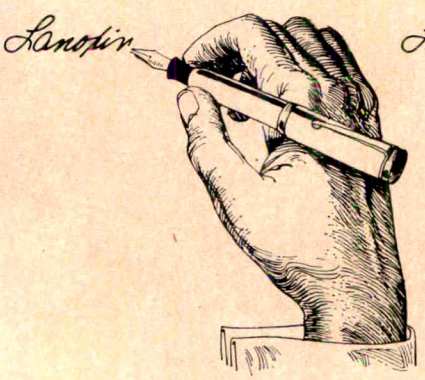
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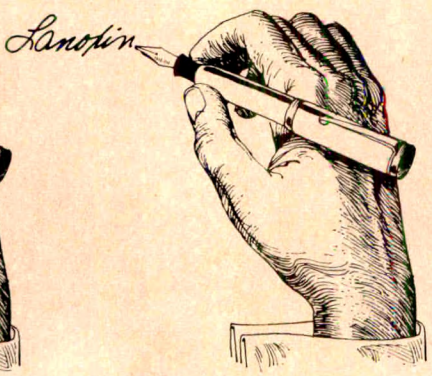
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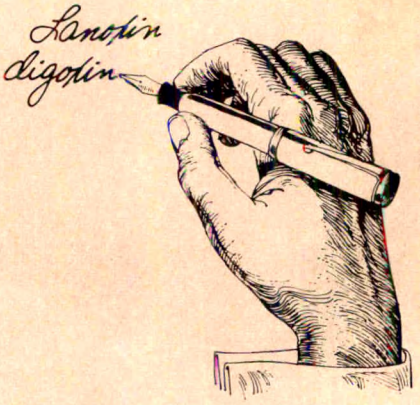
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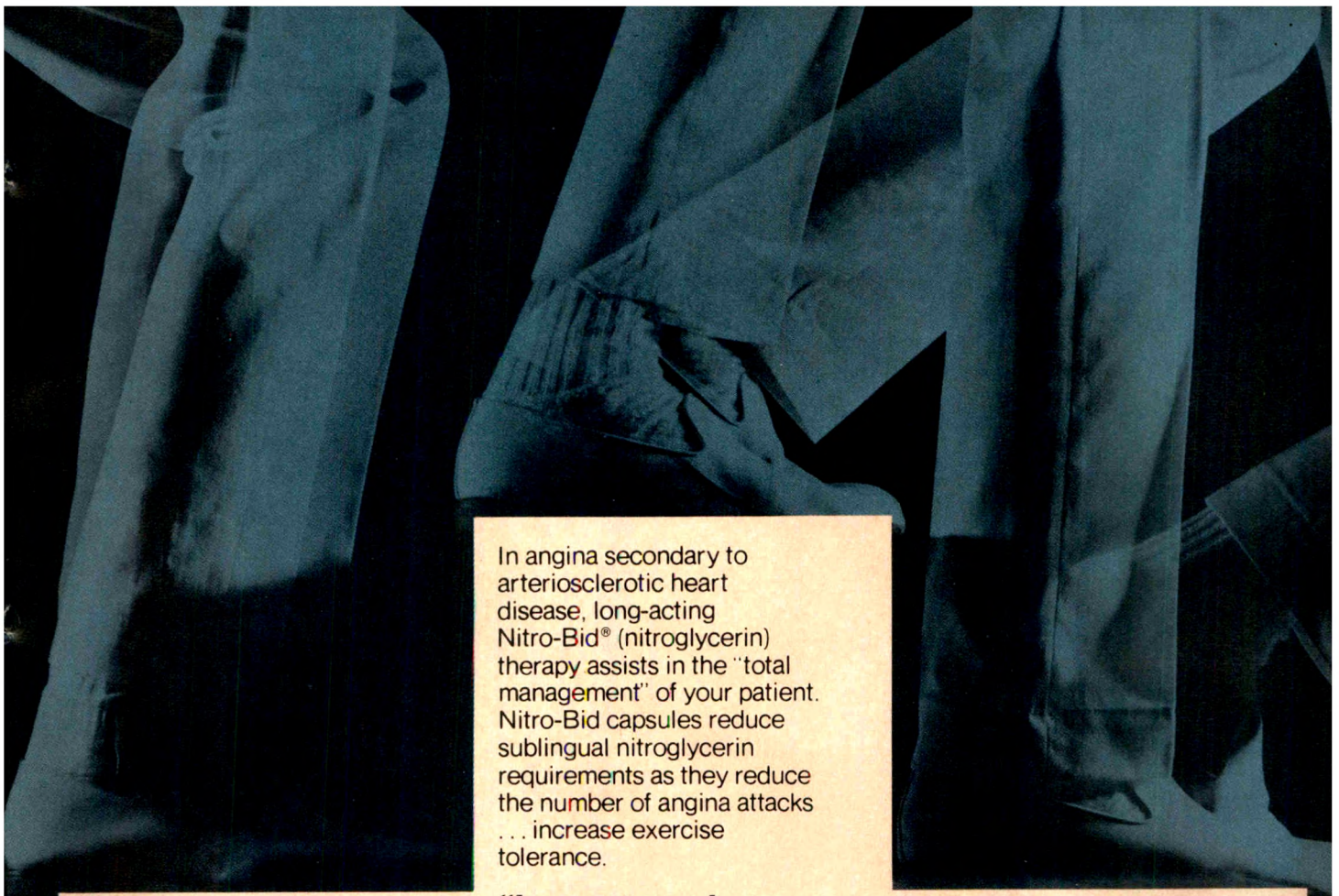

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1. Master, A. M.: The management of angina pectoris. *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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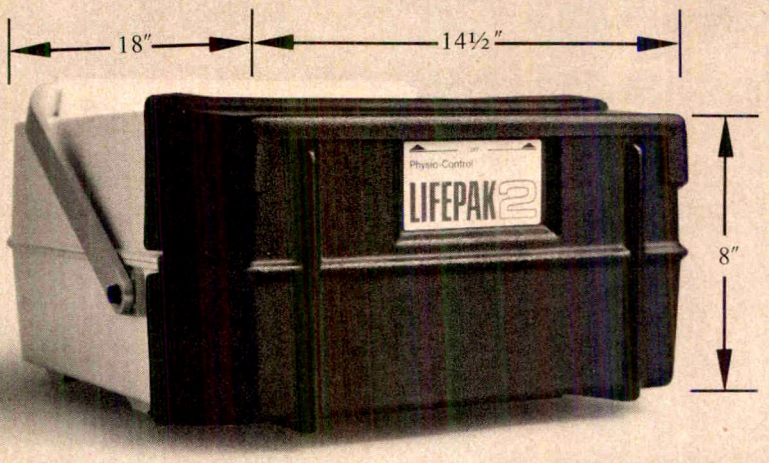

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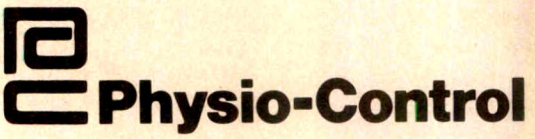

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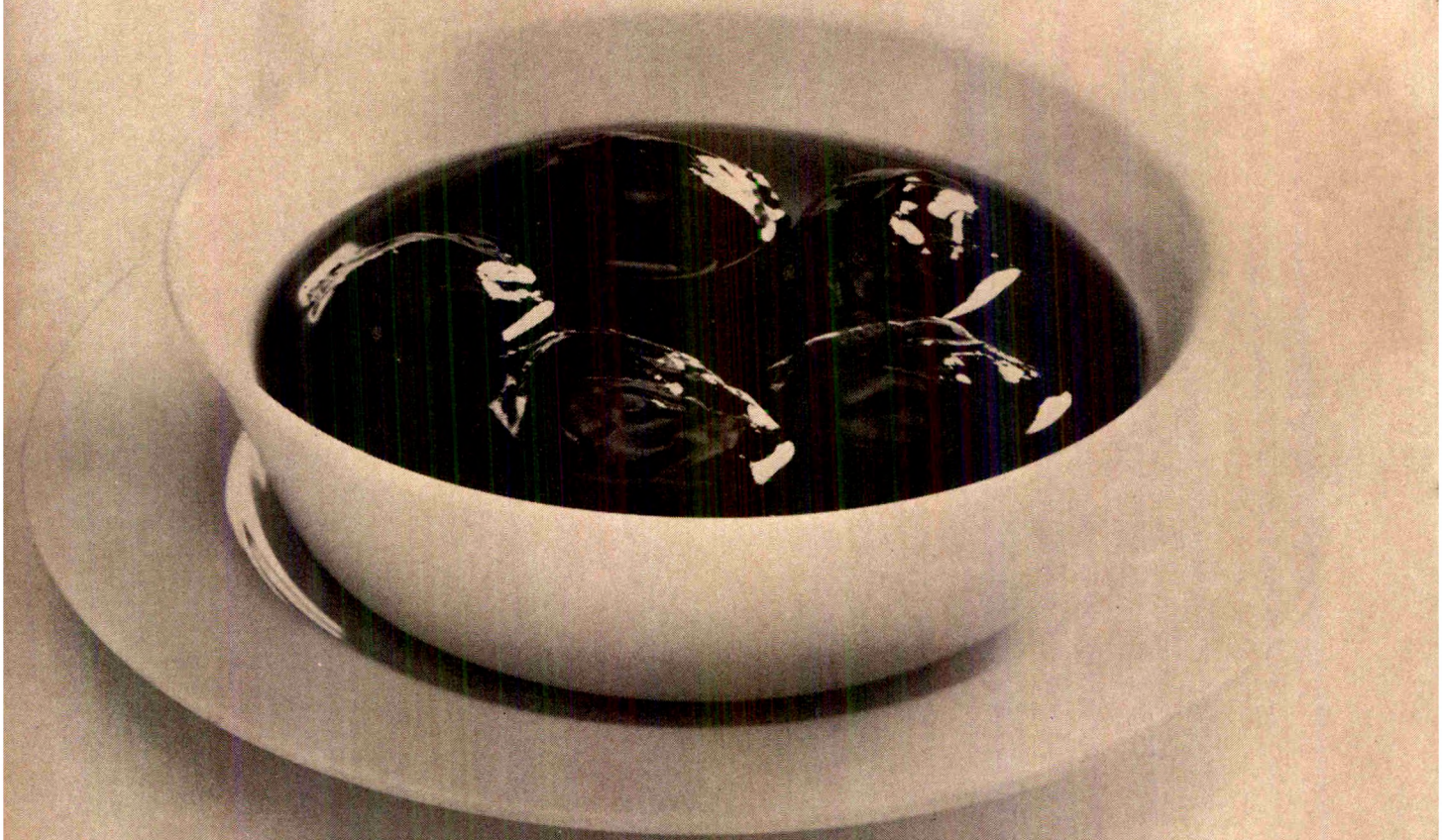

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Addendum

The following are abstracts of papers presented at the 21st Annual Session of the American College of Cardiology, March 1 to 5, 1972, Chicago, Illinois. They should be added to the complete selection of abstracts published in the February issue of the Journal (Amer J Cardiol 29: 250–299, 1972).

Production of Arterial Hypertension by Cadmium

GURDARSHAN S. THIND, MBBS; DARRYL N. BIERY, DVM; KENNETH C. BOVEE, DVM; HARRY F. ZINSSER, M.D., FACC, Philadelphia, Pennsylvania

Cadmium, an environmental trace metal, has been implicated in the pathophysiology of human hypertension. It is thus important to establish whether systemic arterial hypertension can be produced in the dog after cadmium administration. Eight adult female dogs were given 24 intraperitoneal injections of cadmium acetate, 2.0 mg/kg, over 9 months. Determinations of systemic blood pressure, heart rate, cardiac output, and selective renal arteriography and regional renal blood flow and routine hematologic and biochemical studies were serially performed. All dogs completed the study without significant morbidity. There were no significant changes in the mean body weight or results of routine hematologic and biochemical tests.

The mean systemic blood pressure was significantly increased (P value <0.025 to <0.05) in the dogs studied 1 week after the sixth, twelfth, eighteenth and twenty-first cadmium injection. Although no significant blood pressure changes were noted 1 week after the twenty-fourth cadmium injection, significant bradycardia was present (P value <0.005). However, in all of the 4 dogs also studied 3 to 5 weeks after the last cadmium injection, a significant increase in systolic blood pressure (P value <0.01) and bradycardia (P value <0.005) were found. It is concluded that long-term cadmium administration leads to development of persistent arterial hypertension and bradycardia in the absence of obvious signs and symptoms of cadmium overdosage. It is possible that the dog may be the preferred "animal model" for future hemodynamic and other pathophysiologic studies of a noninvasive, chemically induced form of hypertension.

The Effect of Amyl Nitrite on Myocardial Oxygen Extraction in Man With and Without Coronary Artery Disease

EUGENE SANTILLI, MD; HARVEY G. KEMP, Jr., MD, FACC, New York, New York

The action of amyl nitrite (AN) on the coronary circulation of man is unknown. To look for possible vasoactive effects of the drug, oxygen extraction by the myocardium was studied after the administration of AN to 13 subjects, 5 with normal coronary arteries and 8 with coronary artery disease (CAD), as demonstrated arteriographically at the time of diagnostic cardiac catheterization. Paired arterial and coronary venous samples were obtained in a control state and every 30 seconds after AN for 3 minutes and at 5 and 10 minutes. Samples were analyzed for O_2 saturation (O_2 Sat) with the IL-182 CO oximeter. No significant alteration in arterial O_2 Sat was noted. Coronary venous O_2 Sat in normal subjects increased at 30 seconds from 35% Sat (SD 4.0) to 57% Sat (11.7), a rise of 63%, returning to control values by 2 minutes. Subjects with CAD showed a similar response: 35% Sat (SD 4.5) to 61% Sat (SD 9.0), a 71% increase in CS O_2 Sat. Pressure-time per minute, an index of MVO_2, fell approximately 20% in 30 seconds in both groups. These data suggest that coronary blood flow remains high relative to myocardial oxygen needs for about 2 minutes after AN administration, and demonstrate a rapid, primary vasodilating effect of the drug on the coronary circulation of man with and without CAD.

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A Potential Complication of Catheter Tip Transducers

TO THE EDITOR: Traditional hemodynamic variables obtained during cardiac catheterization, such as cardiac output, stroke volume, ventricular end-diastolic pressure, ventricular volume and ejection fraction, are useful for evaluating cardiac performance in terms of its pump function. However, these are not always sensitive indicators of myocardial function and do not truly reflect the inotropic state of the heart muscle. The latter is best evaluated by the force-velocity characteristics of the myocardium as reflected by the maximal velocity of contractile element shortening in the unloaded heart (V_{max})—an intrinsic property independent of ventricular loading.

V_{max} of the intact heart has been derived from experimental animals as well as from clinical investigations by plotting contractile element velocity with instantaneous midwall stress during isovolumic systole, utilizing laborious angiographic analyses of ventricular radii, wall thickness and volume during the cardiac cycle.[1] More recently, a simplified approach has been used utilizing instantaneous isovolumic pressure (IP) and its corresponding rate of rise (dP/dt), and without consideration of tension or wall stress since alterations of ventricular geometry during isovolumic contraction are negligible.[2] Thus, V_{max} has been derived from the general equation: $V_{max} = (dP/dt)/(K \times IP)$, where K represents the series elastic constant of 32 per muscle length at body temperature. Values obtained by both methods have been shown to be highly comparable.[1]

In both methods, a high fidelity pressure recording system is essential for the precise determination of intraventricular pressure and its corresponding dP/dt. This is not obtainable from saline-filled standard catheter external manometer systems, but is reliably available from specially constructed catheter tip micromanometers. Since several prototypes of the latter are now available, it is likely that investigations utilizing this approach including studies in man, will continue to increase.

The purpose of this short communication is to alert the medical community as well as manufacturers of this equipment to a potential hazard of the catheter tip transducer. This became apparent to us after a 2 hour ventricular function study in a dog. At the end of the study, the animal was sacrificed and the catheter micromanometer (1 year old, twice sent back to manufacturer for balancing difficulties and base-line drift, P 866, Statham Instruments Inc.) was pulled back from the left ventricle into the carotid artery without difficulty or resistance. Surprisingly, the micromanometer was missing and, in its stead, the electrical wires were exposed (Fig. 1). Postmortem dissection of the heart, aorta and main branches revealed lodgment of the missing transducer at the origin of the carotid artery. The mitral chordae tendineae were intact.

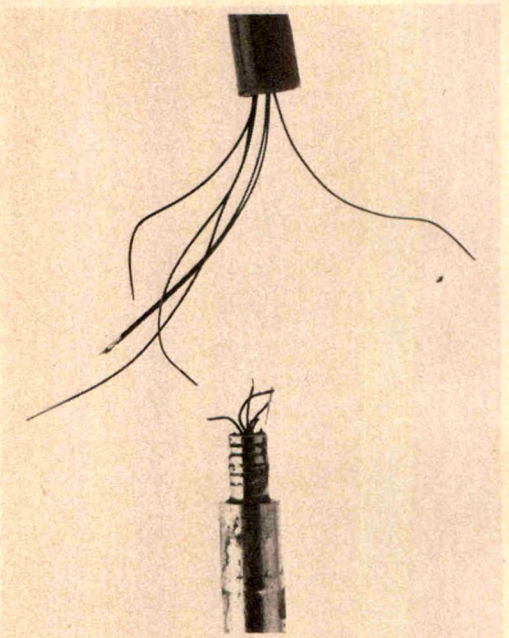

Figure 1. Recovered catheter tip micromanometer (**below**) and the exposed cut wires from the catheter (**above**).

Unfortunately, the dog had already been sacrificed at the time of catheter withdrawal, when breakage may have occurred. The potential complication of such an occurrence in a live subject was therefore not manifested. However, it is obvious that systemic embolization is likely. More importantly, the likelihood of instantaneous ventricular fibrillation resulting from the exposed electrical wires is real. This can be deduced from the schematic diagram (Fig. 2) of a typical catheter tip microtransducer, connected to a recorder, which shows an excitation voltage of 7.5 v.

We are not aware of a similar incident having been reported. Although obviously rare, it is a life-threaten-

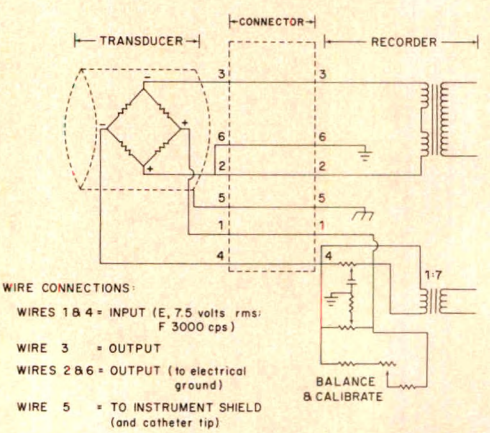

Figure 2. Schematic diagram of electrical connections between micromanometer and recorder.

ing complication which could not be ignored, and should compel manufacturers to provide every assurance possible for a break-free catheter tip transducer. Short of this, it may be necessary to limit catheter usage to a restricted number of studies in human subjects.

This study was supported by Grant RR-305 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

Rene A. Arcilla, MD, FACC
Robert Replogle, MD
Chicago, Illinois

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Propranolol and Quinidine

TO THE EDITOR: I read with interest the paper by Fors et al. on the successful use of propranolol and quinidine in your February 1971 issue.[1] May I draw your attention to earlier reports of similar good results arising from the combined clinical use of these drugs[2–5] and to the experimental studies of the Italian group of investigators confirming these results.[6–7] As Kennedy and West[8] demonstrated that the negative inotropism induced by quinidine administration may turn to positive inotropism at slower heart rates, the theory has been put forward[9] that the beneficial effect of the combination therapy may arise from the bradycardia accompanying the administration of propranolol.

Shlomo Stern, MD, FACC
Jerusalem, Israel

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The Authors Reply

We thank Stern for calling our attention to the excellent paper by Kennedy and West. This study showed that the negative inotropic effect and the alternation in contractile force produced by quinidine was related to quinidine-induced changes in excitability rather than a direct effect of quinidine on contractile processes. The negative inotropic effect and depressed excitability were frequency-dependent, being noted at short beat intervals. At slow heart rates quinidine showed a positive inotropic effect in contrast to propranolol. This is good news for a much maligned drug and confirms the observation that quinidine seldom overtly depresses myocardial function. It was with great misgiving that we began using propranolol and quinidine together knowing that both drugs were supposed to have a negative inotropic effect. The number of patients actually experiencing heart failure with this combination was exceedingly small and could be related almost entirely to the use of propranolol alone, since stopping administration of this drug alone would reverse the signs of failure. These new data support our belief that the fear of using the 2 drugs in combination is unwarranted.

We acknowledge that Stern published the results using propranolol and quinidine in combination in 2 patients in an annotation in October 1966. Our first publication did not appear until October 1967 (Circulation 36: suppl 2: 221, 1967).

E. W. Reynolds, MD
Condon R. VanderArk, MD
William J. Fors, Jr., MD
Ann Arbor, Michigan

Trifascicular Block and Complete Heart Block

TO THE EDITOR: I have read with interest the article by Steiner C, Lau SH, Stein E, et al. (Electrophysiologic documentation of trifascicular block as the common cause of complete heart block, Amer J Cardiol 28:436–441, 1971).

The title indeed suggests that the authors have documented ("proof or evidence to substantiate," Webster's Dictionary) the simultaneous involvement of all 3 segments of the ventricular conduction system in patients with complete heart block. The authors, however, only reiterate the fact, already well known from some of their own previous investigations and those of others, that in patients with acquired complete heart block, His bundle electrocardiography demonstrates that the block is located distal to His potential. I failed to see in their results the actual documentation that proves that the site of block is located in the trifascicular network. Furthermore, in the discussion, they clearly state "When this technique [His bundle electrocardiography] is used it is not possible to be more precise in defining the exact site of block. It may be in the distal common bundle, in the bundle branches or in the peripheral Purkinje system."

This paper confuses further the discussion of complete heart block in that it attempts to provide electrophysiologic documentation for a most interesting concept but fails to do so. It would have been better if this title had been reserved for the publication of re-

sults in a similar group of patients after recording potentials from the left and right bundle branches and His bundle. If this were done and the presence of block distal to the 2 bundle branches documented, then one would have some indirect evidence to suggest the diagnosis of trifascicular block, to the best of our present technical ability.

Jorge C. Rios, MD
Washington, D.C.

The Author Replies

To document means to prove or support (Webster's Dictionary), and our paper is intended to support the other evidence, both pathologic and electrocardiographic, that the common cause of chronic complete heart block is trifascicular block. We went to great lengths in the body of the paper to point out what the limitations of His bundle recording are in this situation, the essence of which is aptly quoted by Dr. Rios. Our conclusion is that this is direct electrophysiologic evidence to support the pathologic and electrocardiographic concepts of trifascicular block.

Dr. Rios' main objection appears to be to our title. I must point out to him that in a title, it is not possible to fully qualify every word. To do so would make the title too long, and this would never be accepted by editors or readers. The full value and qualification of any piece of work can only be assessed by reading the paper.

I agree that it would be of great interest to study right and left bundle branch activity. The latter, however, would require left heart study, which is by no means a totally benign procedure and is not indicated in this group of patients.

Charles Steiner, MD
New York, New York

Book Reviews

A Practice of Thoracic Surgery, third edition, by A. L. d'Abreu, J. Leigh Collis and D. B. Clark. London, Edward Arnold, 1971, 652 pages

It is indeed a pleasure to read this latest edition of Professor d'Abreu's authoritative work, now expanded to include sections on cardiac and esophageal surgery written by his close associates. I found the sections on the "Surgery of Pyogenic Infection and Pulmonary Tuberculosis" and the chapters on "Pulmonary Neoplasms and the Mediastinum" to be excellent and among the best available at this time. This edition continues to present, in a highly personal manner, the view of practicing thoracic surgeons with vast experience.

The introduction contains a good historic review, but I believe that Part I—"Anatomy, Physiology, Patient Selection, Operative Technique, and Post-Operative Care"—is somewhat superficial and inconsistent in its presentation to the serious student of thoracic surgery. The chapters on cardiac surgery are concise yet complete, and the illustrations are pertinent and of good quality. The one defect relates to the inability of the authors of a textbook to discuss fully recent changes in this rapidly changing field, such as open heart surgical techniques in infants, open vs. closed mitral commissurotomy, and currently available prostheses. I assume that the time required to prepare the text necessarily made it impossible to report events occurring during the past 1 to 2 years. I believe, however, that the chapter on cardiac pacemakers is inadequate in the light of present knowledge in this area. "Surgery of the Esophagus" and "Chest Trauma" are presented in a clear, logical and complete manner. In summary, I believe that this book should be available in the library of anyone who is interested in the practice of thoracic surgery.

Gerard A. Kaiser, MD
Miami, Florida

Chest Injuries. Physiologic Principles and Emergency Treatment, edited by Emil A. Naclerio, MD. New York, Grune & Stratton, 1971, 367 pages, $28.50

Indubitably we live in a traumatic environment and, for those called upon to salvage and repair its devastating effects, a sound knowledge of the pathologic processes and a keen understanding of the modalities of treatment are essential. Environmental problems ranging from civil disorders to automobile accidents bring an increasing number of patients into the emergency rooms of our hospitals where, not infrequently, the awareness of the physician who renders immediate care may spell the difference between life and death. This often relates to chest trauma.

The book in question offers a systematic presentation, chapter by chapter, of signs and symptoms, roentgenographic findings, problems in diagnosis and treatment pertaining to thoracic injuries. The approach is schematic and well organized. The subject matter is extensive and varied, including items such as congestive atelectasis, shock lung, respiratory burns, blast injuries and blunt trauma.

There are abundant drawings, charts, photographs and roentgenograms, although some of the latter are not as clear as one may want to see. Pathophysiologic features are stressed. Surgical techniques are not expounded but rather given as broad directives. The most valuable part of the book is that on specific chest injuries; particularly worthwhile is the chapter on "Wounds of the Heart and Great Vessels," with which the author has had considerable experience.

If any criticism is to be made one would say that some fragmentation and repetition exist, but certainly the book is a worthy endeavor from which many a physician—and, one hopes, many patients—will benefit.

George M. Gayola, MD
New Rochelle, New York

Ischemic Forms of Venous Thrombosis by Henry Haimovici. Springfield, Ill, Charles C Thomas, 1971, 230 pages, $25

A comprehensive review of the well documented published cases describing ischemic forms of venous thrombosis is presented in order to provide clarification of the clinical, pathophysiologic and therapeutic aspects of this entity. In contrast to the classic form of venous thrombosis with its relatively benign clinical course, there are instances of phlebitis exhibiting dramatic and sometimes catastrophic circulatory disturbances (phlegmasia cerulea dolens or venous gangrene). "Awareness of such a clinical entity is often the single most important factor leading to its diagnosis." The author uses the term *phlegmasia cerulea dolens* to denote reversible ischemic changes and venous gangrene when there are various degrees of tissue loss. Gangrene usually first appears 4 to 8 days after onset of the ischemic signs. Ischemic gangrene is extremely rare in children.

The clinical picture of both forms of ischemic phlebitis is a combination of venous and arterial symptoms and signs. Cyanosis and edema are the most prominent venous manifestations, whereas absence of peripheral pulses, pain and decreased skin temperature indicate the extent of arterial involvement. The incidence of pulmonary embolism is much greater than in the usual types of thrombophlebitis. Treatment has consisted of elevation, exercises, anticoagulant agents, vasodilating agents, sympathectomy, thrombectomy, fasciotomy and amputation. The mortality rate in the group with phlegmasia cerulea dolens was 16 percent. However, when venous gangrene occurred, the mortality rate increased to 42 percent.

This book presents a comprehensive review of the literature and a detailed study of the clinical course of ischemic venous thrombosis. A detailed bibliography is included. Although this type of phlebitis is uncommon, this study should be valuable to those interested in peripheral vascular disease.

Robert A. Nabatoff, MD
New York, New York

Ischaemic Heart Disease, edited by J. H. deHaas, MD, H. C. Hemker, MD and H. A. Snellen, MD. Baltimore, Williams & Wilkins, and Leiden, The Netherlands, Leiden University Press, 1970, 439 pages

The Boerhaave series on cardiology, held for the last 15 years and intended for postgraduate medical education, is organized by the Faculty of Medicine, University of Leiden, The Netherlands. The meeting on "Ischaemic Heart Disease" was held in English and organized by the Dutch Heart Association.

There are 30-odd chapters in the book, all dealing with lively topics discussed by authorities in each specific field. The first major section, "Aspects of Pathogenesis," discusses the pathology of ischemic heart disease, anatomy of thrombus formation, biochemistry of platelets and thrombus formation, biochemical changes in the myocardium during the reparative processes after coronary artery occlusion, quantitation of enzyme release from infarcted heart muscle, and includes a panel discussion on aspects of pathenogenesis. Discussions by many authorities follow on the epidemiologic approach, diagnostic methods in ischemic heart disease, ischemic heart disease and physical activity, epidemiology and primary prevention and treatment and secondary prevention. In this section and in others, practically every modern phase of coronary disease is well discussed and well illustrated. The book is highly recommended as an excellent reference work for the cardiologist, internist, general practitioner and student. Cross-indexing would have improved the volume by permitting quicker access to specific topics.

Arthur M. Master, MD
New York, New York

Principles and Techniques of Cardiac Pacing, by Seymour Furman, MD and Doris J. W. Escher, MD, with a chapter by Byron Parker. New York, Harper & Row, 1970, 269 pages, $12.50

The development of the pacemaker has revolutionized our knowledge about the management of brady- and tachyarrhythmias. Although basic principles are relatively stable, the hardware and indications for pacing are quickly changing. These experienced authors are indeed courageous to have written a good review of this subject because new concepts are developing with such speed that often a text of this type is outdated before it has reached the desk of the cardiologist, cardiac surgeon, physicians and nurses assigned to the coronary care unit.

This well written book includes a history of the development of pacing, indications for the application of temporary and permanent pacing, management of complications of implanted pacemakers and very practical considerations in the care of these patients. It also contains a critical review of equipment now available and a short discussion of pacemaker electronics that each reader should understand.

The techniques and management of complications are well described and are illustrated by numerous electrocardiograms, roentgenograms and diagrams. The identification of improper pacemaker functions is clearly outlined, and the reader will have no trouble relating his experiences to those of the authors. Each chapter is liberally, but not exhaustively, referenced.

Disappointingly, little if any is written on the subject of pacemaker clinics and transtelephonic monitoring techniques, the hemiblocks, provocative cardiac pacing in the patient with angina pectoris, the techniques for terminating arrhythmias, and new pacemaker models. In spite of these shortcomings, the book serves well to provide an overall view of the changing field as it existed 2 years ago and serves as a very practical guide to the utilization of temporary and permanent pacing.

Bernard L. Segal, MD, FACC
Philadelphia, Pennsylvania

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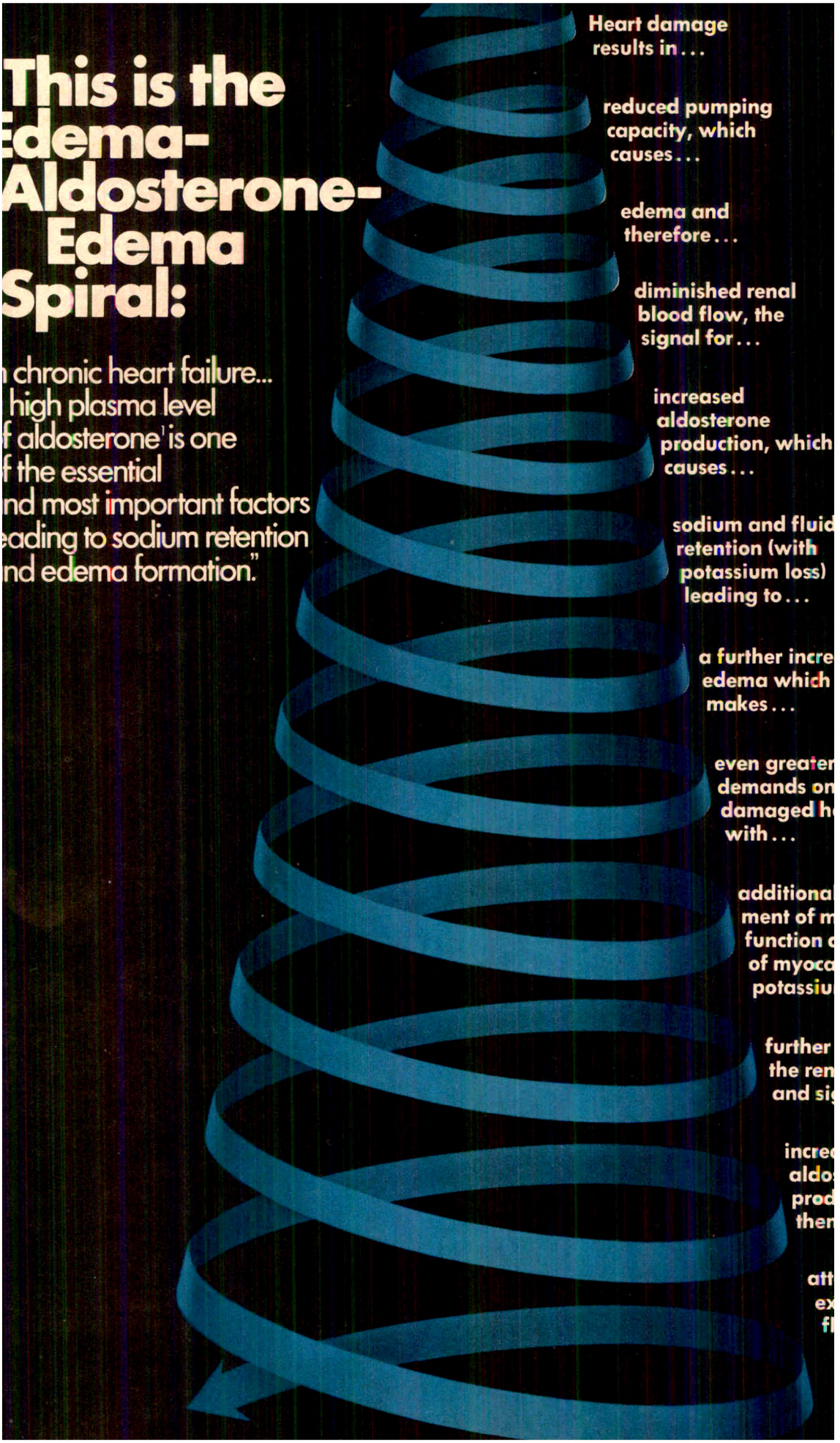
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- Produces a gradual, sustained diuresis which, over a period of weeks, may be greater than that produced[2] with furosemide or ethacrynic acid, while avoiding the dangers of sudden fluid or electrolyte depletion common with fast-acting diuretics.

- Helps prevent digitalis toxicity due to low myocardial potassium levels by helping to retain or restore myocardial potassium through its "...action on the kidney, where it blocks[3] aldosterone action, and perhaps by direct cellular action as well...." In contrast, thiazides, furosemide and ethacrynic acid cause potassium loss which can potentiate[4] myocardial potassium outflow.

- May be combined with other diuretics for an additive effect—permitting lower dosages with each agent while helping to maintain potassium balance.

Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone, particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For **essential hypertension** in **adults** the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For **edema, ascites** or **effusions** in **adults** initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For **children** the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References: 1. Davis, J. O.: Hosp. Pract. **5**:63-76 (Oct.) 1970. **2.** Laragh, J. H.: Hosp. Pract. **5**:43-50 (Nov.) 1970. **3.** Tourniaire, A., and others: Lyon Méd. **223**:707-716 (March 29) 1970. **4.** Seller, R. H.: Quoted in **Medical News** Section, J.A.M.A., **215**:200-201 (Jan. 11) 1971.

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Research in the Service of Medicine

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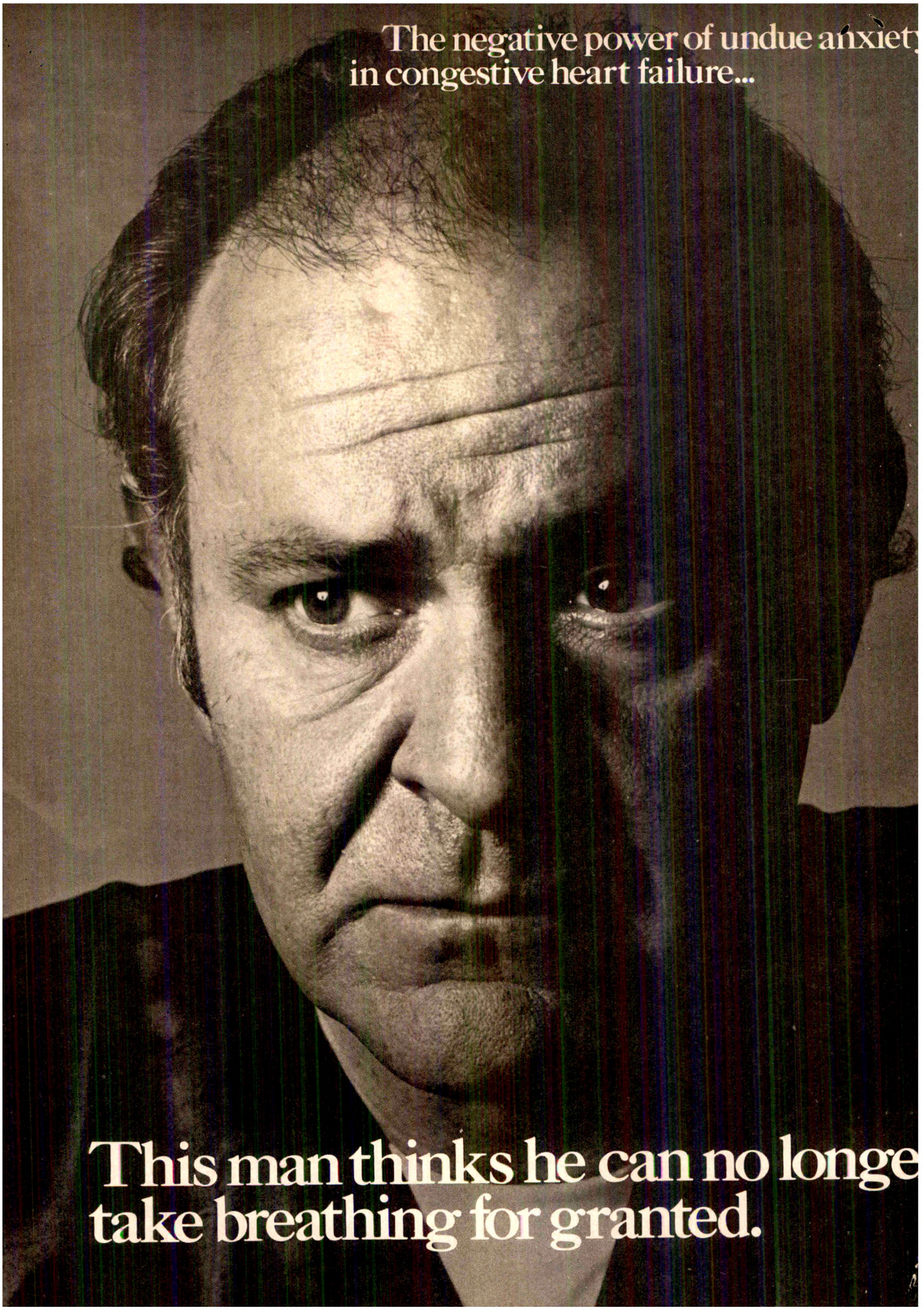
The negative power of undue anxiety
in congestive heart failure...
This man thinks he can no longe
take breathing for granted.

Typical of many patients with congestive heart failure, he also suffers from severe anxiety, a psychic factor that may influence the character and degree of his symptoms, such as dyspnea. His apprehension may also deprive him of the emotional calm so important in maintenance therapy.

Aid in rehabilitation

Specific medical and environmental measures are often enhanced by the antianxiety action of adjunctive Libritabs (chlordiazepoxide). Libritabs can also facilitate treatment of the tense convalescent patient until antianxiety therapy is no longer required. Whereas in geriatrics the *usual daily dosage* is 5 mg two to four times daily, the *initial dosage* in elderly and debilitated patients should be limited to 10 mg or less per day, adjusting as needed and tolerated.

Concomitant use with primary agents

Libritabs is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics, antihypertensives, vasodilators and oral anticoagulants, whenever excessive anxiety or emotional tension adversely affects the clinical condition or response to therapy. Although clinical studies have not established a cause and effect relationship, physicians should be aware that variable effects on blood coagulation have been reported very rarely in patients receiving oral anticoagulants and chlordiazepoxide HCl.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

The positive power of

Libritabs®
(chlordiazepoxide)

5-mg, 10-mg, 25-mg tablets

t.i.d./q.i.d.

up to 100 mg daily

for severe anxiety accompanying congestive heart failure

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A-65

IMPORTANT MESSAGE FOR PHYSICIANS, RESEARCHERS, CLINICAL LABORATORIES, AND PHARMACEUTICAL MANUFACTURERS.

Interested in monitoring digitalis glycoside blood levels?

Whether you're a clinician or researcher interested in monitoring patient digitalization . . .

Or, a clinical laboratory hoping to provide physicians with the most sensitive tool for assessing blood levels of cardiac glycosides . . .

Or, a pharmaceutical manufacturer concerned with the bioavailability of these glycosides in your products . . .

Please note the current availability of four proven, easy-to-use Schwarz/Mann kits for the radioimmunoassay of digoxin (either [^{3}H] or [^{125}I]), or digitoxin (either [^{3}H] or [^{125}I]) which satisfy *all* of the requirements listed above.

A full 186 years after Withering introduced foxglove into clinical medicine for the control of congestive heart failure, one still reads that perhaps 20 to 25% of digitalized patients are actually overdigitalized to the point of toxicity, and that such toxicity now appears to have reached epidemic proportions.(1)

Or one reads a report that claims the mortality rate from overdigitalization ranges from 3% to 21%.(2) And in the same study, 11% of digitalized patients thought to be on adequate daily maintenance therapy were shown to be underdigitalized.

Or one reads of variability in the biological availability of digoxin in commercial preparations along with the suggestion that this may indeed represent a potential hazard to patients.(3)

Or one reads that the FDA is going to launch a digoxin bioavailability program.(4)

Schwarz/Mann—the major factor in radioimmunoassay technology—now provides a practical means for dealing with the problem of monitoring digoxin and digitoxin blood levels: four self-contained kits that offer exceptional sensitivity, specificity, precision, and speed. For detailed information on the practical utility of radioimmunoassay techniques for the determination of glycoside blood levels, please see, for example, references (1), (2) and (3) below. For information on our kits, please use coupon. Thank you.

REFERENCES

(1) "Digitalis Serum Levels: Clinical Use." J. F. Doherty, Annals of Internal Medicine (May, 1971).
(2) "Digitalis Intoxication" G. A. Beller, et al., New England Journal of Medicine (May 6, 1971).
(3) "Variation in Biologic Availability of Digoxin from Four Preparations." J. Lindenbaum, et al., New England Journal of Medicine (Dec. 9, 1971).
(4) "FDA to launch digoxin bioavailability program." FDC Reports (Dec. 20, 1971).

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☐ Other Radioimmunoassay Kits.

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E

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- **Address manuscript** to Simon Dack, MD, American Journal of Cardiology, 466 Lexington Ave., New York, NY 10017.
- **Submit two copies** of all elements of the article: text, references, legends, tables and figures.
- **Arrange the paper** in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- **Number all pages** in above sequence, beginning with title page as 1, abstract as 2, etc.
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THE TITLE PAGE

- **Number title page** as page 1.
- **Include first names,** degrees and, where applicable, FACC for all authors.
- **Insert at bottom:** name and address of institution from which work originated plus information about grants.
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THE ABSTRACT

- **Limit words as follows:** 100 to 250 words for major articles; 50 to 100 words for case reports.
- **Add at end of abstract:** an alphabetical list of 2 to 6 key words and subjects for indexing.

THE TEXT

- **Number pages** in sequence after abstract.
- **Type in duplicate;** double-space.
- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.

- **Cite in numerical** order every reference, figure and table. (Order of mention in text **determines the number** given to each.)
- **Place acknowledgments** at end of text, before references.

THE REFERENCES

- **Type in duplicate;** double-space.
- **Place immediately** after text, and number pages in sequence after text page numbers.
- **Number the references** in order in which they are mentioned in text.
- **Follow the general** arrangement, abbreviations and punctuation styles shown below.

THE FIGURE LEGENDS

- **Start at top** of new page.
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For periodicals, follow INDEX MEDICUS:

31. Bellet S, Feinberg LJ, Sandberg H, et al: The effects of caffeine on free fatty acids and blood coagulation parameters of dogs. J Pharmacol Exp Ther 159: 250-254, 1968

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

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***Indications: Edema associated with congestive heart failure, cirrhosis, nephrotic syndrome and late pregnancy; steroid-induced edema, idiopathic edema and edema due to secondary hyperaldosteronism.**

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When Dyrenium (triamterene, SK&F) is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

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1. Ross, E.J.: Aldosterone and Its Antagonists, *Clin. Pharmacol. & Therap.* 6:65 (Jan.-Feb.) 1965.
2. Earley, L.E.: Edema Formation and the Use of Diuretics, *California Med.* 114:56 (Mar.) 1971.

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DY-202

Dr. Adams

President's Page:
The College and Young Cardiologists

In the President's Page of the July 1971 issue of this Journal, I documented and discussed the phenomenal growth over the past 2 decades of the American College of Cardiology. The total membership of the College has steadily increased from a mere 200 in 1951 to approximately 5,000 in 1972! Throughout this period of growth, the College has steadfastly attempted to maintain a high quality of membership, and this has been accomplished primarily by the excellent work of its Credentials Committee, which carefully reviews each application for membership.

In selecting members for the College, it is assumed that a group of highly qualified cardiologists working together for a common educational purpose best achieves the aims and goals of the College. The word *cardiologist* implies special interest, training and qualification in cardiology whether one is an internist, pediatrician, surgeon, radiologist or basic scientist. The highest recognition of achievement, *Fellowship*, implies that the individual has achieved a significant degree of maturity in cardiology, and that this field is his dominant medical interest. Election to the Fellowship category is recognition of achievement, not of promise.

Since not all cardiologists have demonstrated such an achievement, 2 other categories of membership are available for consideration depending upon such factors as training, recognition of abilities by peers, and age. These are Associate Fellowship and Affiliate. Younger individuals who manifest an interest in cardiology by participation in a training program in cardiology are eligible to apply for the Affiliate category. Once such an individual has completed his formal training in cardiology and is qualified for the subspecialty boards in his field, he is eligible for the Associate Fellowship category. All applications, of course, must be sponsored by Fellows of the College.

Membership in the College has several practical advantages: subscription to the American Journal of Cardiology, no registration fee for attendance at the Annual Meeting of the College, reduced fees for attendance at Regional Continuing Education Programs, reduced subscription charge for the ACCESS audio tape journal, and receipt of College news. The American College of Cardiology needs the contributions of the younger cardiologists for its continued growth and programs of education. I encourage the younger cardiologists to apply for membership in the College.

In concluding this final President's Page of my term of office, I extend a warm welcome to Dr. Samuel M. Fox III, who will be installed as the new President this month.

Forrest H. Adams, MD, FACC
President, 1971–72
American College of Cardiology

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

MAR. 20–22 **Electrocardiographic Interpretation of Arrhythmias: A Physiologic Approach.** Charles Fisch, FACC, director, Indiana University Medical Center, Indianapolis, Ind.

MAR. 20–25 **Consultants' Course in Cardiology.** Simon Dack, FACC, Arnold M. Katz, FACC and Robert S. Litwak, FACC, directors. Mount Sinai School of Medicine, New York, N. Y.

APR. 3–12 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 5–7 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 12–13 **The Total Coronary Care System—The Community and The Hospital.** Sylvan L. Weinberg, FACC, William G. Cassel, FACC, C. W. Imm and Joseph M. Wilson, FACC, co-directors. The Sheraton-Dayton Hotel, Dayton, Ohio.

APR. 17–20 **Current Concepts in Cardiology 1972.** Philip R. Akre, FACC and John A. Bower, MD, directors. Riviera Hotel, Las Vegas, Nev.

MAY 8–12 **The Medical and Surgical Treatment of Cardiovascular Disease.** J. Willis Hurst, FACC and W. Dean Warren, MD, directors. Co-sponsored by ACC and Council on Clinical Cardiology of the American Heart Association. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 12–13 **Computer Applications in Electrocardiography.** C. A. Caceres, FACC, director, Sheraton Park Hotel, Washington, D. C.

MAY 18–19 **Heart Sounds and Murmurs: An Audiovisual Presentation.** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, Ind.

MAY 25–27 **A Critical Approach to Cardiovascular Diagnosis.** Arthur Selzer, FACC, director. Jack Tar Hotel, San Francisco, Calif.

SEPT. 9–11 **Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC and R. O. Davies, co-directors. Queen Elizabeth Hotel, Montreal, Quebec, Canada.

SEPT. 11–13 **A Symposium for Cardiac Nursing.** Fred D. Ownby, FACC, director. Nashville, Tenn.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director and Yoshio Watanabe, FACC, co-director. Hahnemann Medical College, Philadelphia, Pa.

OCT. 2–4 **When, Why and How in Clinical Cardiology.** Charles Fisch, FACC and Borys Surawicz, FACC, co-directors. Marion County General Hospital, Indianapolis, Ind.

OCT. 5–6 **Acute Myocardial Infarction—Pre Hospital Phase.** John B. Johnson, FACC, director. Washington, D. C.

OCT. 10–14 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director: Mountain Shadows Hotel, Scottsdale, Ariz.

OCT. 17–19 **Coronary Care Units and the Mobile Coronary Care Unit.** William J. Grace, FACC, director. St. Vincent's Hospital and Medical Center of New York, New York, N. Y.

OCT. 26–28 **Diagnostic and Therapeutic Approach to Cardiac Arrhythmias.** Edward K. Chung, FACC, director. The Greenbriar, White Sulphur Springs, West Va.

NOV. 3–5 **Cardiology 1972.** T. K. Lin, FACC, director. Honolulu, Hawaii.

NOV. 6–15 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

DEC. 8–10 **Title not available.** Henry I. Russek, FACC, director. Americana Hotel, New York, N. Y.

1973

JAN. 14–16 **A Perspective on New Techniques in Congenital and Acquired Heart Disease.** John H. K. Vogel, FACC, director and Bruce C. Paton and Leslie L. Kelminson, FACC, co-directors. Opticon Theater, Snowmass at Aspen, Aspen, Colo.

MAR. 16–18 **Noninvasive Methods in Cardiology — Apexcardiography, Phonocardiography, Pulse Tracings and Phonoarteriography.** Samuel Zoneraich, FACC, director. Queens Medical Center, Jamaica, N. Y.

APR. 2–11 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

Advance registration forms for these courses may be obtained by writing to Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Advance Programs

MAY 25–27, 1972

San Francisco, California

A Critical Approach to Cardiovascular Diagnosis

Sponsors:
The American College of Cardiology
and
Pacific Medical Center
San Francisco, California

Conference chairmen:
ARTHUR SELZER, MD, FACC
KEITH COHN, MD, FACC
San Francisco, California

Educational director:
ROGER SHEPHERD, MD
San Francisco, California

Audience: The course is aimed at cardiologists and other clinicians with special interest and experience in cardiovascular diseases.

Educational objectives: It will be assumed that participants are familiar with diagnostic uses and criteria of the commonly used methods of examination: history, physical examination, electrocardiography and roentgenography. The course will thus focus upon: (1) selection of diagnostic criteria with the best sensitivity and specificity and identification of those criteria most likely to lead the diagnostician astray; (2) establishment of diagnostic uses of newer techniques (for example, echocardiographic techniques and stress testing); (3) a critique of the positive contribution and the limitations of invasive diagnostic methods: cardiac catheterization, angiocardiography, arteriography; and (4) consideration of when, in the course of various disease entities, invasive techniques are indicated.

Organization of material: Rather than discuss each diagnostic method by itself, the subject matter will be presented from the point of view of common cardiac problems. Each half-day session will be devoted to a disease or a group of related clinical problems. Within the context of each disease, the appropriate diagnostic techniques will be discussed in depth.

Methods of presentation: The plenary session will de-emphasize didactic lectures. Each session will include the participation of 5 to 6 faculty members who will cover the important diagnostic methods applicable to the disease under discussion. The individual problems will be defined and the issues identified by those with special expertise in the field who will cover them in depth and detail. Exchange of ideas among speakers will be invited regarding controversial points.

In addition, the three luncheon periods will be devoted to programmed workshops dealing with case exercises. The appropriate material will be sent to registrants in advance of the course. These luncheon sessions will be conducted in groups of ten and will serve to reinforce the important ideas from the plenary session.

Evaluation: A self-test dealing with the important points to be covered in the course will be sent to each registrant in advance. Registrants will be requested to hand in this completed test at the time of registration for the course. This pre-test will help each registrant identify those aspects of the conference of special value to him. A similar test will be administered near the end of the conference. This will permit each registrant to monitor his own progress and will help the faculty to assess the effectiveness of the course and to plan future courses.

Guest faculty: Drs. S. Gilbert Blount, Denver, Colo.; J. David Bristow, Portland, Ore.; J. Michael Criley, Torrance, Calif.; Mervin J. Goldman, San Francisco, Calif.; E. William Hancock, Stanford, Calif.; Joseph K. Perloff, Washington, D.C.; and Richard Popp, Stanford, Calif.

Local faculty: Drs. William L. Anderson, William T. Armstrong, Ian Carr, Nora F. Goldschlager, Leonard Karpman, Masanobu Kamigaki, John J. Kelly, Manly F. Langston and Robert W. Popper

Enrollment:
Minimal and maximal enrollment has been established for this program. Advance registration is requested.

Fee:
ACC members, $120; nonmembers, $170. A limited number of spaces will be reserved for cardiology fellows and residents at a reduced fee of $60.

* Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Candidates Certified

The following candidates were certified in the subspecialty of cardiovascular disease on October 22–23, 1971, Palo Alto, Calif.

Arizona

Tucson
Schocket, Lee I.

California

Downey
Alexander, John D.

LaJolla
Myers, James W.

Long Beach
Allen, William H.
Ellestad, Myrvin H.

Los Angeles
Salzman, Stephen H.

Oakland
Stullman, Walter S.

Redwood City
Weinstein, Belson J.

Sacramento
Bonanno, Joseph A.

San Bruno
Rabbino, Michael D.

San Francisco
Abbott, Joseph A.
Beckmann, Charles H.
Forde, Thomas P.
Scheinman, Melvin M.

San Pedro
Wyman, Milford G.

Santa Barbara
Urquhart, Robert R.

Sepulveda
Yankopoulos, Nicholas A.

Tustin
LeVine, Richard B.

Connecticut

Bloomfield
Ritvo, Arnold S.

New Haven
Wolfson, Steven

Colorado

Denver
Spicer, Melvin J.

Florida
Miami
Sayfie, Eugene J.
Miami Beach
Zaron, Stephen J.
Miami Lakes
Martinez, Alvaro I.

Illinois
Evanston
Bernstein, Ira J.

Massachusetts
Boston
DeSanctis, Roman W.

New York
New York
Stringfellow, Charles A.

Ohio
Canton
Kamen, Alan R.
Cincinnati
Abbott-Smith, Charles W.

Utah
Logan
Sorensen, John L.

Personals

THOMAS J. RYAN, MD, FACC, Boston, has been appointed chief of the newly formed department of clinical cardiology at the University Hospital, a part of Boston University Medical Center. Dr. Ryan was formerly chief of cardiology at St. Elizabeth's Hospital, Boston.

The Mayo Foundation Board of Trustees has announced plans for the September 1972 opening of a four-year Mayo Medical School in Rochester, Minnesota. RAYMOND D. PRUITT, MD, FACC, a leader in the development of the school, will become the school's first dean and chief executive officer. In addition to his duties, Dr. Pruitt will remain director for education in the Mayo Foundation.

Two Meetings in Singapore

The Council on Epidemiology and Prevention, International Society of Cardiology, announces its Fifth Ten Day International Teaching Seminar on Cardiovascular Epidemiology, September 24 to October 6, 1972, in Singapore. Nominees should be at the postdoctoral level, with some residency training or its equivalent. Nominations should be submitted by chiefs of departments or institutions, and should be accompanied by a personal letter of application for the nominee, together with his curriculum vitae. The deadline for applications is April 1, 1972. They should be sent to Jeremiah Stamler, MD, Secretary, Council on Epidemiology and Prevention, ISC, Room LL 139, Chicago Civic Center, Chicago, Ill., 60602.

•

The Fifth Asian-Pacific Congress of Cardiology will be held October 8 to 13, 1972 in Singapore. The American College of Cardiology and the American Heart Association have made arrangements for a variety of group travel plans for those planning to attend the Congress. For further information write American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Cardiovascular Teaching Day

Participants of the Seventh Annual Cardiovascular Teaching Day at St. Peter's Hospital, Albany, N. Y. discuss the program with Raymond Harris, MD, FACC, chief, Subdepartment of Cardiovascular Medicine, St. Peter's Hospital and program chairman. **Left to right:** Sol Sherry, MD, FACC, professor and chairman of the Department of Medicine at Temple University School of Medicine, Philadelphia, Pa.; Ray W. Gifford, Jr., MD, FACC, head of the Department of Hypertension and Nephrology, Cleveland Clinic Foundation, Cleveland, Ohio; George E. Green, MD, assistant professor of surgery, New York University Medical School and associate attending surgeon at St. Luke's Hospital, New York, N. Y., and Dr. Harris.

Postgraduate Course on Exercise Testing and Training

The Medical Rehabilitation Research and Training Center of The George Washington University Medical Center together with The American College of Cardiology, American Heart Association and The Social and Rehabilitation Service of the Department of Health, Education and Welfare will co-sponsor a week-long postgraduate course entitled "Exercise Testing and Training in the Care of Cardiac Patients and Coronary Prone Subjects: Principles, Techniques, Applications and Effects" at Airlie House near Warrenton, Virginia from April 16 through April 21, 1972. Registration is limited to 150 enrollees and is open to physicians and associated health personnel working in the area of exercise and heart disease. The course will be co-directed by Herman Hellerstein MD, FACC, Cleveland, Ohio and John Naughton, MD, Washington, D.C. For further information write Dr. John Naughton, Director, Division of Rehabilitation Medicine, 2150 Pennsylvania Ave., N.W., Washington, D.C. 20037.

Paul Dudley White Symposium

The photograph **at left** shows part of the overflow audience of 1,003 physicians attending the Paul Dudley White Symposium: Major Advances in Cardiovascular Therapy held at the Americana Hotel in New York City December 10 to 12. The record registration marks an all-time high for ACC-sponsored continuing education programs. At **right,** program director Henry I. Russek, MD, FACC is shown congratulating Dr. White, who holds the plaque awarded to him at this meeting. The plaque read as follows: "The American College of Cardiology and St. Barnabas Hospital award this citation to Dr. Paul Dudley White, distinguished physician, gifted teacher, noted scientist, world statesman for unparalleled achievement in cardiovascular disease. 'Your spark has illuminated the darkness and united all mankind in a common goal.' "

Obituaries

Samuel Bellet, MD, FACC

SAMUEL BELLET, MD, FACC, Philadelphia, Pa., was born in Russia on August 21, 1902 and died on December 13, 1971. He was graduated from the Jefferson Medical College in 1925. He spent 1927 to 1934 in training in the disciplines of pathology, physiology, research surgery and clinical cardiology. During these years, he was also engaged in full-time training in the basic sciences, research and some teaching in undergraduate studies. Included were visits to various medical centers in New York, Boston, Cleveland, London and Paris to gain knowledge of techniques and disciplines used in cardiology.

Dr. Bellet was assistant cardiologist, Philadelphia General Hospital from 1927 to 1935; Fellow of the Robinette Foundation, University of Pennsylvania, 1928 to 1934; member of the staff of the Robinette Foundation; associate cardiologist, Philadelphia General Hospital from 1935 to 1950; director, Division of Cardiovascular Diseases, Graduate School of Medicine of the University of Pennsylvania from 1948 to 1963; professor of Clinical Cardiology, Graduate School of Medicine of the University of Pennsylvania from 1954 until his death; and lecturer in pharmacology, University of Pennsylvania School of Medicine; and director, Division of Cardiology, Philadelphia General Hospital, from 1951 until his death.

Dr. Bellet's lectureships included a lecture under the auspices of the Rockefeller Institute, Paris, in 1955 entitled, "The Effects of Electrolytes on the Electrocardiogram with Particular Reference to Potassium," and in 1957, the Malcolm Rodgers Lecture on Cardiac Arrhythmias, University of Wisconsin. In 1962 he was awarded the American Specialist Grant by the Department of State in cooperation with the American College of Cardiology to visit Israel and Turkey to demonstrate the latest techniques in cardiology. He was given a grant to establish a cardiovascular institute in Karachi, Pakistan and was a member of the President's Commission on Heart Disease, Cancer and Stroke from 1964 to 1965.

Dr. Bellet was a consulting editor of the *American Journal of Cardiology* at the time of his death and had served as associate editor of the Journal from 1959 to 1964. He served as associate editor of the *American Heart Journal* from 1945 to 1950 and later as an editorial consultant. He was associate editor of *Circulation* and editor of its Abstract Section from 1945 to 1956 and a member of the Editorial Board from 1957 to 1962. He had been a member of the Editorial Board of the *Journal of Electrocardiography* since 1968. He became a Fellow of the College in 1958, and served a term as a member of the

Board of Trustees of the College; in 1971 was named College Governor for Eastern Pennsylvania. He was a Fellow of the American Association of University Professors and the American College of Chest Physicians. He was a member of the American College of Physicians, American Medical Association, American Heart Association, Heart Association of Southeastern Pennsylvania, Philadelphia College of Physicians, Sigma XI; New York Academy of Sciences, the American Physiological Society and the Federation of the American Societies for Experimental Biology. He previously had been president of the Heart Association of Southeastern Pennsylvania, and chairman of the Medical Advisory Board, Athletic Commission, State of Pennsylvania.

Dr. Bellet was author of approximately 325 articles and numerous books, the most recent being the third edition of Clinical Disorders of the Heart Beat, published in August 1971. He conducted extensive research and study on cardiac arrhythmias, the effects of smoking and caffeine on the heart, the effects of various pharmacologic agents and other variables on the heart, including the stress of automobile driving.

He is survived by his widow Mrs. Jean Rosenthal Bellet, and his daughter Joan, 2021 Spruce St., Philadelphia.

FRANCISCO L. RAFFUCCI, MD, FACC was born in Rincón, Puerto Rico on January 4, 1921 and died October 14, 1971. He received his BS degree from the University of Puerto Rico in 1940 and his MD degree from the University of Maryland in 1943. He completed his internship at the St. Agnes Hospital in Baltimore, Md. in 1944, and served in the Army of the United States as a battalion surgeon from 1944 to 1946, receiving the Bronze Star for meritorious services. He did his postgraduate work in surgery at the University Hospital of the School of Tropical Medicine in San Juan and at the University Hospital of the University of Minnesota from 1946 to 1951, obtaining the degree of MSc in surgery from the University of Minnesota in 1951. He was certified by the American Board of Surgery in 1952 and became a Fellow of the American College of Surgeons in 1954. In 1952, he joined the Department of Surgery of the School of Medicine of the University of Puerto Rico as assistant professor of surgery and was appointed head of the department of surgery in 1961.

Dr. Raffucci was consultant in surgery to the San Juan City Hospital, the San Juan Veterans Administration Hospital and other important hospitals in Puerto Rico. He was a member of several distinguished professional societies, including the Puerto Medical Association, the American Medical Association, the Association of American Medical Colleges, the New York Academy of Sciences, the American Association for the Advancement of Science, the International Society of Surgery and the American Society of Thoracic Surgeons. He was selected to the American Surgical Society in 1966 in recognition of his outstanding contribution as a leader and investigator in cardiovascular surgery. He was elected a Fellow of the American College of Cardiology in 1968.

The members of the Puerto Rico chapter of the American College of Cardiology regret the passing of this distinguished Fellow of the College and most appreciated friend.

ELI A. RAMIREZ, MD
ACC Governor for Puerto Rico

VIRGINIUS D. MATTIA, MD, FACC, died on July 4, 1971 at the age of 48. A graduate of Rutgers University and the New York Medical College, Dr. Mattia interned and served as associate attending in cardiology at the St. Barnabas Medical Center in Newark. He was also chief of investigative medicine at the Clara Maas Medical Center, Belleville, N. J. Dr. Mattia's principal interest was in the pharmaceutical industry. From 1953 to 1956 he served as the associate editor for the Merck Manual

Virginius D. Mattia, MD, FACC

and as manager of the medical literature department for Merck and Company. In 1957 he joined Hoffmann La-Roche as director of medical information. After a series of promotions, he became president and chief executive officer in January 1966. Under his leadership, his company achieved unparalleled scientific and commercial success. In spite of his heavy responsibilities, he served as president of the New Jersey College Fund Association, chairman of the Rutgers Medical School Advisory Commitee and trustee to Rutgers University. He was a participating member of many scientific and medical associations besides the College. He served as president of the Essex Co. (N. J.) Heart Association from 1961 to 1963. His commitment to science was evidenced by the support his company provided to many basic and clinical projects throughout the United States and the development of the Roche Institute for Molecular Biology in Nutley. I had the privilege of working in the environment he created.

Dr. Mattia is survived by his widow, Alice Ann Mattia; his four children, Peter, Gail, Mark and Barney; his mother, Mrs. V. D. Mattia, Sr.; and his sister Mrs. Kenneth Rosa.

WILLIAM B. ABRAMS, MD, FACC
ACC Governor for New Jersey

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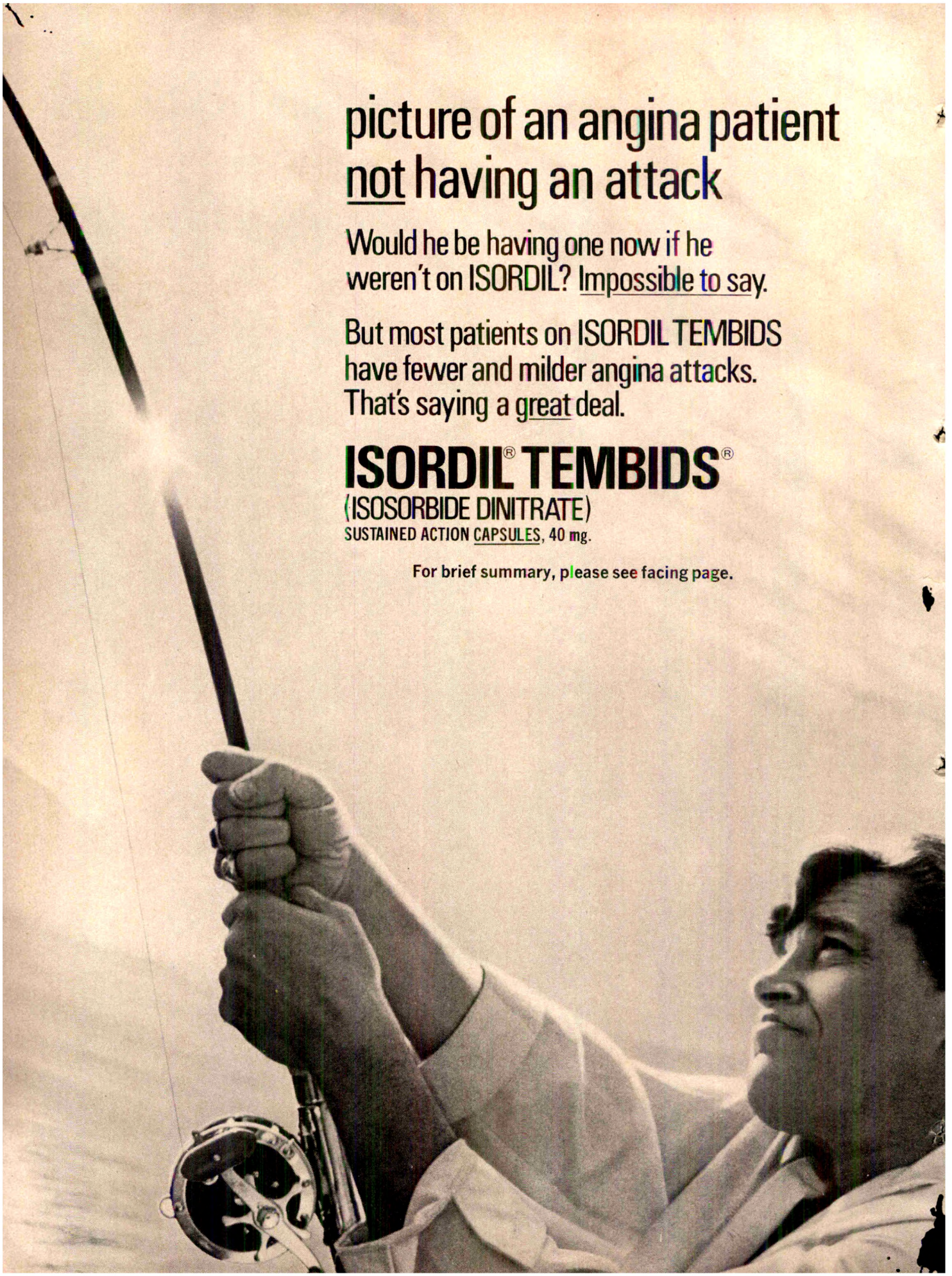

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Careful consideration of dosage schedule in hypothyroid patients with cardiac disease is required, and the drug should be withdrawn or dosage reduced if aggravation of angina, increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops. Hypothyroid patients are more sensitive than euthyroid patients, especially if treated concomitantly with other thyroid preparations. Special consideration must be given to the dosage of the hypothyroid patient.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias or coronary insufficiency. Drug withdrawal or careful observation of patients receiving such injections is recommended, especially before elective surgery. In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and subsequent readjustment if dextrothyroxine is later withdrawn.

USAGE IN WOMEN OF CHILDBEARING AGE: Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of Choloxin to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

PRECAUTIONS: Unusually high PBI values are common in treated patients and are not evidence of hypermetabolism. In children, use only when a significant cholesterol-lowering effect is observed. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism and thus more common in the hypothyroid patient, especially the hypothyroid cardiac. Cardiac changes have rarely been precipitated in non-cardiac patients: Angina pectoris (0.2% incidence), arrhythmia (0.5%), myocardial ischemia (<0.1%), cardiomegaly (<0.1%), fatal and non-fatal myocardial infarctions (<0.2%): Insomnia, nervousness, palpitations, tremors, weight loss, lid lag, sweating, flushing, hyperthermia, hair loss, changes in bowel habits, diuresis, and menstrual irregularities may also be related to the metabolic action. A few patients developed itching and skin rashes, apparently from iodism.

Dyspepsia, nausea and vomiting, and changes in appetite occurred in less than 1%. Headache, changes in libido, hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain and bizarre complaints were reported in less than 1% of treated patients. Gallstones were newly discovered in 13 patients, and cholestatic jaundice in one, although relationship to drug therapy was not established. In a total of 19 patients, pre-existing peripheral vascular disease, exophthalmos, retinopathy, and disturbed sensorium continued to worsen. Cerebrovascular accidents, thrombophlebitis, and G.I. hemorrhages each occurred in less than 1% of patients, but there appears to be no relationship to dextrothyroxine therapy. In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

DOSAGE RECOMMENDATIONS: For *adult* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is 4.0 to 8.0 mg. per day. The initial daily dose should be 1.0 to 2.0 mg. to be increased in 1.0 or 2.0 mg. increments at intervals of not less than one month to a maximum level of 6.0 to 8.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol. When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients, the more conservative dosage schedule is recommended.

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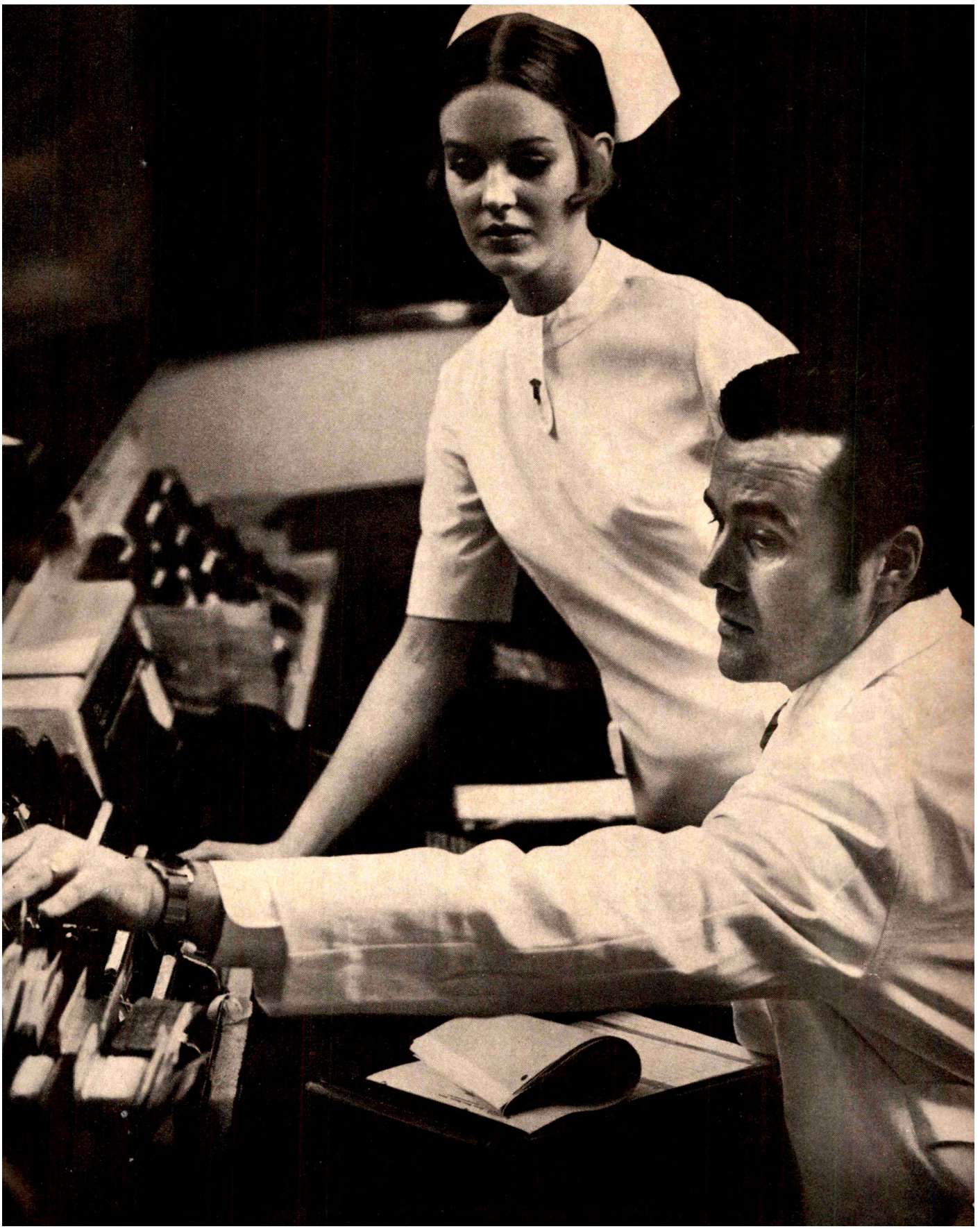

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Iwao Moriyama
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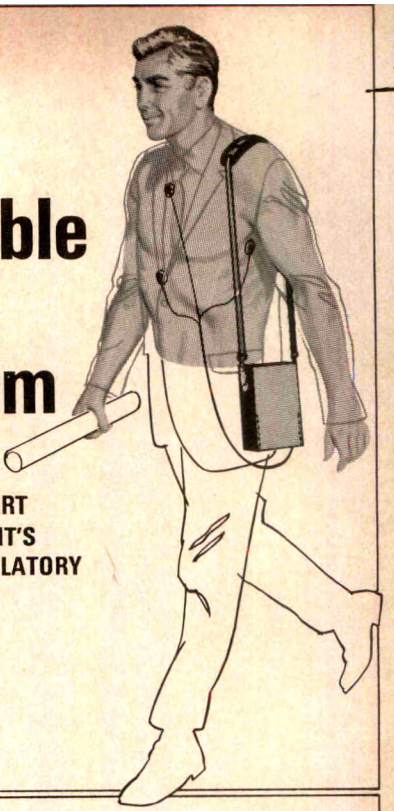

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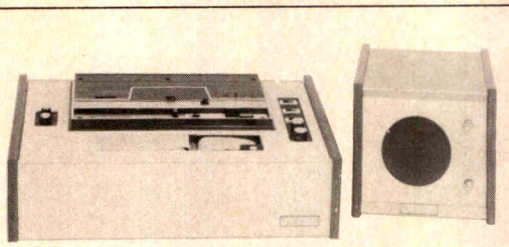

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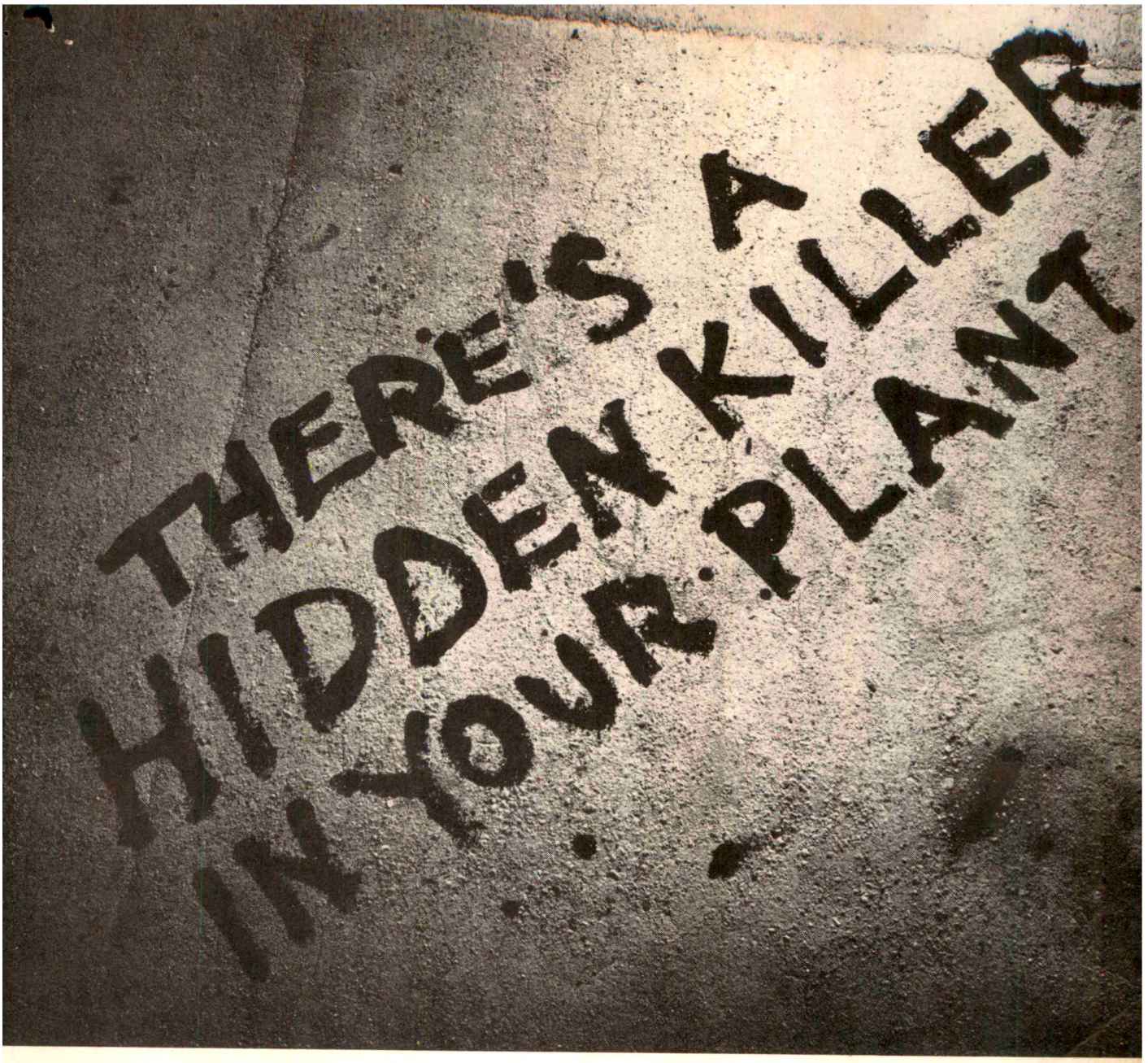

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